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Implementation of Risk Based Monitoring into Academic Led Clinical Trials in Ireland

A thesis submitted to the National University of Ireland, Cork
for the
degree of Doctor of Philosophy in the School of Public Health, UCC

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LIST OF ABBREVIATIONS

AACODS	authority, accuracy, coverage, objectivity, date and significance checklist for grey literature
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRF/Cs	Clinical Research Facilities/Centres
CRO	Contract Research Organisations
CTIMP	Clinical Trials of Investigational Medicinal Products
CTTI	Clinical Trials Transformation Initiative
CTU	Clinical Trial Unit
EC	European Commission
ECC	European Economic Community
ECRIN	European Clinical Research Infrastructure Network
EDC	Electronic Data Capture
EI	Enterprise Ireland
EMA	European Medicine Association
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRAMMS	Good Reporting of a Mixed Methods Study
HPRA	Health Protection Research Authority
HRB-CRCI	Health Research Board-Clinical Research Coordination Ireland
ICH-GCP	International Conference on Harmonisation -Good Clinical Practice
IMP	Investigational Medicinal Product
ISM	Issue Management System
ISV	Independent Software Vendors
MCC	Metrics Champion Consortium
MDTT	Multidisciplinary Testing Teams
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC	Medical Research Council
NASA TLX	NASA Task Load Index
OECD	Organisation for Economic Co-operation and Development
OPTIMON	OPTimisation of MONitoring for clinical research studies
PI	Principle Investigator
PK	Pharmacokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
QI	Quality Improvement
RBM	risk based monitoring
REC	Recognized Ethics Committees
SaaS	Service as a System
SAE	serious adverse events
SDV	Source data verification
SOP	Standard Operating Procedure

SQUIRE	Standards for Quality Improvement Reporting Excellence
SWAT	Study within a Trial
US	United States
WHO	World Health Organization

DECLARATION

I declare that this thesis has not been submitted for another degree either at University College Cork or elsewhere. The work, upon which this thesis is based, was carried out in collaboration with a team of researchers and supervisors who are duly acknowledged in the text of the thesis. The Library may lend or copy this thesis upon request.

Signed Date

ACKNOWLEDGEMENTS

I get by with a little help from my friends

STATEMENT OF CONTRIBUTION

This thesis consists of four manuscripts, two that are published and two that will be submitted for publication in the coming months.

Exception to sole authorship:

Chapter 3: Hurley C, Shiely F, Power J, Clarke M, Eustace JA, Flanagan E, et al. Risk based monitoring (RBM) tools for clinical trials: A systematic review. Published in *Contemporary clinical trials*. 2016;51:127.*https://www.ncbi.nlm.nih.gov/pubmed/27641969*

Chapter 4: Hurley C, Sinnott C, Clarke M, Kearney P, Racine E, Eustace J, et al. Perceived barriers and facilitators to Risk Based Monitoring in academic-led clinical trials: a mixed methods study. Published in *Trials*.2017;18(1):423.*https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2148-4*

As lead author of these chapters, I was responsible for conceptualizing the study design, carrying out data collection and analysis, and drafting and submitting manuscripts. My co-authors provided guidance during each step of the research and provided feedback on draft manuscripts.

Under the guidance of my supervisors, I also prepared the remaining chapters in this thesis. Chapters five and six will be submitted for publication to scientific journals and Chapters One, Two and Seven were not written for publication.

THESIS ABSTRACT

Introduction

In November 2016, the International Conference on Harmonsation (ICH) published a requirement for sponsors to develop a systematic, prioritised, risk-based approach to monitoring clinical trials. This process is more commonly known as Risk Based Monitoring (RBM). However, evidence suggested that a gold standard validated approach to RBM did not exist and it was unclear how sponsors would introduce RBM into their clinical trials units (CTUs).

In 2014, Ireland, unlike countries such as Switzerland and the UK, did not have a national strategy to support the introduction of RBM into its publicly funded, academic-led CTUs. The absence of a national strategy and gold standard RBM approach meant it was not clear how RBM would be implemented in CTUs. Therefore, the overarching aim of this thesis was to develop, implement and evaluate a quality improvement intervention to support the introduction of RBM into academic-led clinical trials in Ireland.

Methods

This thesis employed a multi-method research strategy directed by the Knowledge to Action (KTA) framework over four years from October 2014 to October 2018. The KTA framework is a conceptual framework to assist the translation of knowledge into sustainable, evidence-based interventions. This thesis used a range of research methods, implemented in four separate sequential phases, to address different components of the KTA framework which primarily involve knowledge creation and knowledge translations.

The four phases first involved systematically reviewing the existing evidence of RBM methods. Then, in a mixed method study, I explored the attitudes, and perceived barriers and facilitators to the implementation of RBM in academic-led clinical trials in Ireland. Next, I did a document analysis study to examine the experience of monitoring in a clinical trial. Finally, I developed the quality improvement study by combining the results of the three earlier phases to identify the most appropriate

quality improvement intervention to support RBM use in academic led clinical trials in Ireland.

Results

The systematic review showed several tools exist to support the implementation of RBM. The mixed methods study showed a need for training and regulatory endorsed guidelines to support the implementation of RBM in academic-led clinical trials. The document analysis showed that on-site and centralised monitoring can be used simultaneously to fulfil ICH GCP's seventeen monitoring requirements. The findings of these three studies were combined and a brief, face-to-face, interactive education workshop was identified as an effective way to encourage RBM tool usage among clinical researchers working in academic-led clinical trials in Ireland.

Conclusion: Applying the KTA framework to empirical data has led to an intervention that is implementable in clinical practice and has the potential to positively change monitoring practices of clinical researchers. This thesis provides critical evidence on the complexities associated with implementing RBM in academic-led clinical trials. It provides practical recommendations to guide clinical researchers who wish to perform RBM.

Chapter 1. Introduction

1.1 Chapter overview

The National Institute of Health defines clinical trials as research studies in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.(1). Such interventions include new medicines, but also new therapies, devices, diagnostic techniques and surgical procedures, as well as optimising existing medicinal products and procedures to promote better health and welfare(1, 2). Globally, each year, millions of Euros, time and resources are spent conducting thousands of clinical trials that aim to discover new treatments for diseases as well as new ways to detect, diagnose, and reduce the risk of disease(3-5). These clinical trials are only possible thanks to the thousands of participants who volunteer to take part in these trials(6).

Fortunately, most clinical trial participants, experience mild or no adverse events during their time in a trial(7). However, there have been cases where clinical trial participants have been hurt by the intervention or trial procedure(8, 9). This is inevitable as clinical trials involve the testing of new medicines and therapies with unknown safety profiles that may unexpectedly harm trial participants(2, 10). Therefore, to ensure the rights and wellbeing of participants are protected, it is essential that trial activity is adequately monitored, and the trial complies with relevant regulation and the approved trial protocol(11, 12).

Clinical trial can be divided into Clinical Trials of Investigational Medicinal Products (CTIMPs) and non CTIMPs(13). Food trials, social and psychological interventions that target complex social and behavioural problems are examples of non -CTIMPs. Unlike CTIMP, which are subject to clinical trial regulations that require some degree of monitoring, non-CTIMPs, do not legally require monitoring. Primarily for this reason, most of the existing literature and guidelines for safety monitoring and reporting of adverse events focuses on CTIMPs(13, 14). Consequently, there is little monitoring guidance for investigators conducting non- CTIMPs (social and behaviour trials)(15).

However, despite the lack of a legal obligation and guidance, participant safety and data integrity are of extreme importance in non CTIMPs(14). Like CTIMPs, risks such as participants entering non- CTIMPs without giving fully informed consent and implications of incomplete and inaccurate study data, exist in non-CTIMP trials (14). In recent years, many researchers have started to acknowledge the risks associated with non -CTIMPs and are employing the use of Data and Safety Monitoring Boards (DSMBs) to monitor the progress and quality of these trials(16). It is claimed that the safety of study participants in non-CTIMPs has increased due to the activity of DSBMs(16).

However, this Thesis will only focus on the monitoring of CTIMPs trials which is enforced under the EU Clinical Trial Directive(17).Traditionally, clinical trial monitoring involved intensive on-site monitoring visits at clinical trial sites and exhaustive source data verification of clinical trial data (12, 18-20). In recent years clinical researchers have questioned the validity and necessity for traditional monitoring methods (19, 20). Many consider it to be an expensive, time-consuming and resource heavy activity that does not improve the quality of clinical trial data or the protection of trial participants (21, 22). Regulatory agencies, such as the International Committee for Harmonization and the Food and Drug Administration, are now advising clinical researchers to stop automatically applying the traditional 100% source data verification approach and instead use risk-based monitoring (RBM)(12, 23, 24). It is suggested that RBM will reduce clinical trial costs by reducing the use of unnecessary traditional monitoring activity that has little impact on the safety or quality of a clinical trial(25).

The RBM method is founded on the premise that each trial is different with its own risks that require a bespoke monitoring strategy(12). It focuses on the individualized prevention or mitigation of likely sources of error or potential harm within each individual trial(12, 26). As such, the RBM approach is an adaptive approach to clinical trial monitoring that focuses monitoring on the identified areas which have the most potential to impact participant safety and data quality(26). Accordingly, a RBM plan

must be tailored to the risk profile of each clinical trial(10). To do this, first, before a trial begins a robust risk assessment of the trial must be conducted to identify risks within a trial(10, 26). Once the risks have been identified comprehensive, accurate monitoring guidelines are needed to guide the mitigation of the identified risks(10, 26). RBM tools and methodologies have been developed to guide the development of an RBM plan(27, 28). However, their effectiveness and usability has not been proven and so a gold standard approach to RBM does not exist(27).

The non-prescriptive nature of RBM, lack of evidence-based methodology and lack of evidence to show its superiority to traditionally monitoring has hindered its widespread adoption(29, 30). Consequently academic sponsors are struggling to implement RBM in their trials (29, 31, 32). Furthermore, in Ireland, unlike countries such as Switzerland and the UK, a national strategy to support the introduction of RBM into its publicly funded, academic-led clinical trials units does not exist (23). The aim of this Thesis is to develop, implement and evaluate a quality improvement intervention to support the introduction of RBM into academic led clinical trials in Ireland.

The aim of this chapter is to discuss the evolution of RBM and challenges regarding its implementation into academic led clinical trials. This chapter will also discuss the overall aim of the Thesis and provide an overview of the subsequent Thesis chapters.

1.2 Clinical trials – phases, staff and academic trials

1.2.1 Clinical trial phases

One of the first documented clinical trials was conducted in 1747, by Dr James Lind. The aim of his trial was to find a cure for scurvy among an unrandomized, unblinded, convenient study sample of twelve sailors(1, 33). In the last three centuries, clinical trial methodology has greatly evolved(1). Major developments include the introduction of the placebo concept in 1863 to compare the effect of an active treatment to a dummy remedy(1). To the 1940s, when the Medical Research Council (MRC) in the UK, developed the double-blind controlled trial and random allocation process(1, 33). Then, by the 1970s randomized controlled trials were widely

recognized as the gold standard for establishing the safety and efficacy of medical interventions(33).

Randomised clinical controlled trials involve the comparison of the action of an experimental treatment to the untreated progression of an illness in a patient under study(33). To generate unbiased, accurate and generalisable findings from a randomised clinical controlled trial, the study is conducted under tightly controlled conditions. Under these conditions, it is possible to conclude that an improvement or deterioration in a patient's illness is caused by the treatment being administered(2). For findings of the randomised clinical controlled trial to be considered accurate, it is vital that the administration of the experimental treatment is the sole difference between the experimental (group that receives the study drug) and the control group (group that receives the placebo or standard care)(33). This is facilitated by the random, concealed allocation of the intervention to study participants (34). Accordingly, patients' entering a trial are assigned to either the experimental or the control group following a non-predictable, chance-based procedure, and the patient, the investigators and the participating physicians are ideally blinded to which group (experiment or control) the patient has been assigned(35). The procedure of random and concealed allocation of study groups has the primary objective of removing subjective interferences, for instance, the possibility that investigators assign healthier patients to one arm of the study leading to allocation bias(34, 35).

The scientific quality of the randomised clinical controlled trial methodology is currently considered the gold standard in treatment evaluation(33). Over the past several decades, randomised clinical controlled trial have prevailed over clinical judgement, case reports, and observational studies as evidential standards in medicine development and evaluation(33). Furthermore, during this time frame, randomised clinical controlled trial became a crucial part of the regulatory process whereby a new medicine could only gain marketing authorisation and access to the drug market after its safety and effectiveness was proven in typically 2 substantial Clinical Trial of an Investigational Medicinal Product (CTIMP)(36).

Currently, randomised , controlled clinical trials are large and tightly regulated projects that must comply with ethical and regulatory requirements while at the same time maintaining high scientific standards(11, 37). The clinical trial process is long, expensive and resource intensive. It can take up to fifteen years and sometimes over a billion dollars to get an Investigational Medicinal Product (IMP) approved for patient use (38, 39). Clinical trials of new IMPs are conducted in four separate clinical trial phases (I-IV) that follow an orderly and deliberate progression that build on one another (Table 2) (38, 39). Each phase is designed to answer certain questions about the IMP under investigation. For example, the aim of a Phase I trial is to examine the safety profile of an IMP on a small number of study participants(40). While the aim of a Phase III trial is to determine if the IMP, now with a preliminary safety profile, has a therapeutic effect(40).

Table 1: Clinical trial phases

Phase	Purpose
I	First stage of IMP testing in human participants. Designed to determine the maximum amount of the IMP that can be given to healthy volunteers (between 2-100) before adverse effects become intolerable or dangerous
II	Designed to evaluate whether the IMP has any biological activity or effect and continue phase I safety assessments, performed on between 100-300 participants
III	Designed to assess how effective an IMP is in practice. They are the most expensive, time-consuming and difficult trials to design and run. They require many participants with a specific medical condition (300–3,000) and are often multi-centre, international clinical trials
IV	Designed to monitor the safety of an IMP after it has received marketing authorisation by the appropriate regulatory agencies such as the European Medicine Association (EMA) in the EU or the FDA in the US. Marketing authorization permits the sale of an IMP on the open

	market. Typically, a phase IV trial is conducted over a minimum of two years, to monitor the safety of the IMP on the open market(40)

All clinical trials, regardless of their phase, pose a risk to participant's health as each trial is trying to establish the safety and efficiency of a pharmaceutical molecule by administering it to human subjects(12, 28). Depending on the characteristics of a clinical trial, its risks might be trivial causing only mild temporary discomfort; or serious causing long-term consequences(41). Side effects of a clinical trial can be physical (death, disability, infection), psychological (depression, anxiety) and economic (job loss)(42, 43). Therefore, before clinical researchers can start a clinical trial, they must first conduct a risk assessment analysis to ensure that the potential patient and societal benefits of a trial are proportionate to, or outweigh, the risks imposed on study participants(11, 41). For example, most CTIMPs are designed to exclude women of childbearing age, pregnant women, or women who could become pregnant during the study(44, 45). In some cases, the male partners of these women are also excluded or required to take birth control measures(44, 45). These is because researchers do not know what impact the IMP would have on a fetus and so the risks of including women of childbearing age in a trial far outweighs the potential benefits(44, 45).

Once a trial begins, it is vital that all four clinical trial phases are adequately monitored as safety risks for participants are present throughout all phases(38, 39). The purpose of monitoring as specified in GCP clearly highlights the need to ensure the three following aspects are achieved: the safety and well-being of the patient, the quality of the data and compliance with regulatory requirements(11). However, it must be noted that monitoring is limiting and cannot overcome inherent quality issues in a clinical trial(46). Clinical trial monitoring is defined by the International Conference on Harmonisation as *'the act of overseeing the progress of a clinical trial,*

and ensuring that it is conducted, recorded and reported in accordance with the protocol, SOPs, Good Clinical Practice (GCP), and the applicable regulatory requirements', and aims to protect the rights and well-being of trial participants, while ensuring protocol compliance and data integrity(11). However, there are many well documented cases of research misconduct involving the deliberate fabrication or falsification of clinical trial data that were not detected by clinical trial monitoring (47, 48). For example, in 1999, the Food and Drug Administration in the USA, granted marketing authorisation for rofecoxib, a nonsteroidal anti-inflammatory drug(49). This meant that doctors could prescribe rofecoxib to their patients(49). However in 2004, during the phase IV follow up trial, rofecoxib was withdrawn from the market as researchers identified an increased risk of heart attack and stroke associated with patients long term use, high dosage use of rofecoxib (49). These risks had been overlooked during phase I–III trials(49).

Conducting a clinical trial involves a diverse group of stakeholders including research sponsors (industry, academia), clinical investigators, patients, study nurses, pharmacists, laboratory technicians, physicians, and regulators. Each stakeholder offers a different set of tools to support an essential component of a clinical trial(47). Along with time, money, materials (e.g., medical supplies), support systems (informatics) and a clear plan for completing the necessary steps in a trial. Therefore monitoring cannot be expected to correct clinical trial errors created by incompetent study teams, lack of resources such as budget and inadequate protocol design (47, 48).

1.2.2 Clinical trial staff

All four clinical trial phases follow a formal trial protocol which describes the objectives, design, monitoring requirements, statistical considerations and aspects related to the organization of that trial(50). Effective design and implementation of a trial protocol requires the involvement of many different types of research staff and medical professionals(51). Consequently, clinical trial staff are one of the most important, yet expensive, components of a clinical trial (50, 52). A typical clinical trial team will include a sponsor, principle investigator, study nurses, data manager,

monitor, biostatistician, administration staff ,pharmacists and most importantly study participants (11, 53) (Table 2). As stated by ICH GCP guideline, 'everyone involved in conducting research should be qualified by education, training and experience to perform his or her respective task(s)'(11).

Table 2: Roles and responsibilities of a clinical trial team(11, 52)

Role	Responsibility
Sponsor	Institution, organisation or group of organisations with overall responsibility for initiation, management, insurance and financing arrangement for the trial
Principal Investigator (PI)	Responsible for the ethical conduct of the trial and for compliance with relevant legislation and ICH GCP guideline
Trial coordinator	Manages and conducts the day-to-day study activities in accordance with the protocol, applicable regulations and ICH GCP requirements.
Study participant	Comply with study requirements and fulfil other obligations they undertake when they make an informed choice to enrol in the trial
Research nurses	Provide clinical care for the participant, obtain participant's informed consent and ensure the protocol is being followed at each step of the trial
Data managers	Oversee development of data collection tools based on the clinical trial protocol. Ensures trial data is collected, validated, and stored security.
Trial monitor	Ensure the trial team complies with the protocol by checking clinical site activities during on-site visits and communicates findings with the PI
Sub-investigators such as clinicians	Individuals authorized to make medical judgments and decisions regarding study participants
Statistician	Design protocol and Statistical Analysis Plan (SAP) to describe the statistical techniques for study analysis in detail.
Pharmacists	Ensure IMPs are appropriate for use and are procured, handled, stored and used safely and correctly.

Overall, responsibility for protocol compliance and safety of study participants is shared between the local site Principle Investigators (if different from the sponsor), the various Research Ethics Committees that supervise the trial and the regulatory agency for the country where the IMP will be authorized(23). Each Principle Investigator must be qualified by training and experience and should have adequate resources to properly conduct their trial(54). A Principle Investigator completes this role by formally delegating trial tasks to appropriately trained individuals and ensures that these individuals have the required GCP and protocol-specific training required for their specific roles and responsibilities(54, 55). In addition, a Principle Investigator must document and monitor all staff duties in an up to date, accurate and complete delegation log(23, 55).

The trial sponsor is responsible for ensuring that formal processes are in place to maintain oversight of all delegated functions in a clinical trial(56, 57). They take responsibility for the management and financing of a clinical trial but in some cases may not conduct the trial(23, 56). ICH GCP guideline, section 5.1.1 states that a sponsor is responsible for selecting the investigator(s) and/or institution(s) that manage the day to day running of a trial(23). It is also the sponsor's responsibility to establish an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial(58).

1.2.3 Academic clinical trials

Historically academic institutions initiated, sponsored and managed the first clinical trials (51). Unlike pharmaceutical sponsored trials, academic clinical trials are usually motivated by public health need and scientific opportunities that would not offer substantial monetary gains(59). Primarily, academic sponsored studies mostly involved the assessment and evaluation of the therapeutic effects, safety and socio-economic implications of both new indications for licenced IMPs and innovative treatment within the real conditions of the health systems(60). However with the development of large global pharmaceutical companies and with the enormous costs

of drug development, there has been a progressive decrease in academic regulated clinical trial activity (61-63).

In recent years, Irish academic institutes have united to increase the number of academic sponsored clinical trials been conducted in Ireland. Since 2012, the five largest Irish Universities; University College Cork, National University of Ireland Galway, Royal College of Surgeons Ireland, University College Dublin and Trinity College Dublin, have taken on the role of clinical trial sponsor(64). Accordingly, they have the legal authority to oversee the financial and management responsibilities of academic sponsored or led clinical trials(64). The five universities delegate their sponsor responsibilities through their own Clinical Research Facilities/Centre (CRF/C)(64). The five CRF/Cs in Ireland, actively collaborate between Universities and industry and manage all aspects of a clinical trial from clinical trial documentation, to participant recruitment, study monitoring and data analysis (64). They are facilitated by the Health Research Board-Clinical Research Coordination Ireland (HRB-CRCI), established in 2014 to provide independent, centralized support in the conduct of multi-center clinical trials across Ireland(64). To date, the CRF/Cs have sponsored numerous clinical trials (64). These trials are primarily financed by public funding such as EU's Seventh Framework Programme (FP7), the Irish Health Research Board (HRB) or the Science Foundation Ireland (SFI)(64, 65).

It is widely noted that Irish academic sponsored clinical trials have the potential to improve patient care and save lives(66). A strong academic clinical research infrastructure gives Irish people access to lifesaving trials and in 2018 the Irish Health Research Board committed €11.6 million to ensure that this continues to happen(67). In May 2018, the Irish clinical trials infrastructure network was showing growth at a steady pace with 237 trial sites opened across the Irish network, up from 134 in 2014 when HRB-CRCI was first established (67). There trials are led by a team of over 330 clinical investigators(68).

Although many clinical trials are still performed in a single country, over the years there has been a trend to perform large-scale, multi-site international clinical trials(10, 32). These international, collaborative trials facilitate the fast recruitment

of large sample sizes by recruiting participants from multiple geographical locations and ethnicity, which also enhances the external validity of a trial(69). However, despite its many advantages, the rise in international multi-site clinical trials has also increased the complexity of conducting clinical research(10, 69). These issues are not as inhibiting for larger pharmaceutical companies, who have the resources to manage this complexity (66, 70). Such resources are not normally available to academic sponsors who often run a clinical trial under a small, restrictive public funding grant(70).

Furthermore, pharmaceutical companies often have divisions in the different countries where a multi-centre trial is being performed, giving them access to local expertise and native language speakers(71). In addition, many pharmaceutical companies employ multinational Contract Research Organisations (CROs) to conduct their clinical trials (63). Such arrangements are often extremely expensive. Whereas academic sponsors, who in most cases are performing trials on small public funding grants, cannot afford outsourcing their trial to a CRO(71). Thus, academic sponsors of clinical trials in many instances, due to lack of funding, infrastructure and experienced permanent staff; have great difficulties dealing with the requirements of performing large, multi-centre international trial(32, 70).

1.3 Clinical trial ethics

The goal of a clinical trial is to develop new knowledge and insight that will hopefully improve human health(1). This knowledge is generated by determining if new drugs and treatments are safe and effective by testing them on volunteer human participants(2, 40). However, before a clinical trial can begin, the researchers must first decide if the benefits of the new drug or therapy under investigation outweigh its risks to participant safety(23). For example, a new therapy may be associated with greater efficacy for patients but also an unacceptable level of adverse medical outcomes for study participants(40, 72). Moreover, once a trial begins it should be terminated early if the risk-benefit relationship changes and the risks to study participants outweigh the benefits (73).

Nevertheless, by placing some people at risk of harm for the good of others, clinical research has the potential to exploit study participants(72). The Hippocratic Oath, historically taken by all physicians, states that doctors must first 'do no harm' to their patients(74). Moreover, this principle forms the basis for clinical trial ethics, by which clinical researchers must endeavour by all reasonable means to ensure that no harm comes to study participants and to preserve the integrity of the science of the trial(72, 74). However a clinical researcher who is motivated by scientific discoveries may be tempted to jeopardize their participant's safety by enrolling them in a clinical trial where its risks outweigh the benefit for that participant (75, 76). Thus human subjects could potentially be put at risk for the benefit of others which make exploitation inherently possible in all stages of a clinical trial (77-81).

The ethical concerns of clinical trials have been debated for as long as clinical trials have been conducted and unfortunately research involving human subjects has a corrupt past(82, 83). Historical evidence has documented many examples of ethical misconduct in clinical trials(76, 84). For example, the term 'human experimentation' will forever be linked to the unprincipled clinical trials conducted by the Nazis on war prisoners in early 1940, during World War II and the Holocaust(85). These trials were a series of medical experiments performed on large numbers of prisoners, including children, in Nazi concentration camps. Nazi physicians forced prisoners to participate in trial that typically resulted in death, trauma, disfigurement or permanent disability(85). These experiments are now considered examples of medical torture and have greatly influenced the development of ethical standards for clinical trials.(85).

The Tuskegee Syphilis Study is another example of an unethical clinical trial(76, 84). This study was conducted by the United States Public Health Service in collaboration with Tuskegee University, between 1932 and 1972(76, 84). The study aimed to track the natural progression of untreated syphilis and to determine the best treatment options(84). The researchers recruited over six hundred thousand impoverished African-American farmers from Alabama(84). Most participants had syphilis before they were recruited to the trial(84). The 40-year study was entirely unethical, as researchers knowingly failed to treat patients with penicillin when it was found to be

an effective cure for the disease in the 1940s(76). This trial is citied as the most scandalous biomedical research projects in US history (84).

Arising out of such clinical trial abuses were the development of ethical guidelines; created to assist clinical researchers to conduct ethical research(85, 86) (see Figure 1). The Nuremberg Code, published in 1947, was the first major international document to provide guidance on research ethics(85). It made voluntary participant consent mandatory for all clinical trials. It required researchers to use appropriate study methods and not to conduct a trial if its risks outweighed its potential benefits. It also states that a clinical trial should be based on previous knowledge (e.g., data derived from animal experiments) that justifies the trial to be performed on human subjects (82).

Unfortunately, despite the introduction of the Nuremberg Code in 1942, in the 1960s new medicines were still licenced for patient use without supporting clinical trial evidence(85). The thalidomide disaster in 1962 is one such example. Without clinical trial evidence, thalidomide became an over the counter drug for the treatment of morning sickness in pregnant women(87). Shortly after the drug was sold, thousands of infants worldwide were born with limb malformation(87). In response to the thalidomide disaster, the U.S Congress enacted the Kefauver-Harris Amendment to the Food and Drug Cosmetic Act in 1962. This amendment required new drugs be proven efficacious in 'adequate and well -controlled investigations'(33, 88). By 1970, the Food and Drug Administration (FDA) interpreted the amendment as requiring randomised controlled, double blind clinical trials for the approval of new pharmaceuticals(88, 89). The Council of the European Economic Community (EEC) soon implemented similar regulations(90).

By the end of the 1970s most countries had their own regulations and guidelines for conducting, reporting and evaluating clinical trial data(90)To overcome global inconsistencies, in clinical trial guideline for trial conduct, in 1996 the International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) published the guideline for Good Clinical Practice E6 (R1)(11). This guideline is more commonly known as the ICH GCP guideline(11, 91).

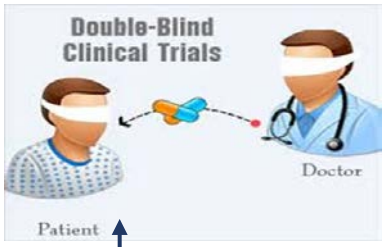
Figure 1: Evolution of Clinical Trial ethics

Dr James Lind conducted the first clinical trial to find a cure for scurvy

1747

1868

Dr Austin Flint introduced the placebo

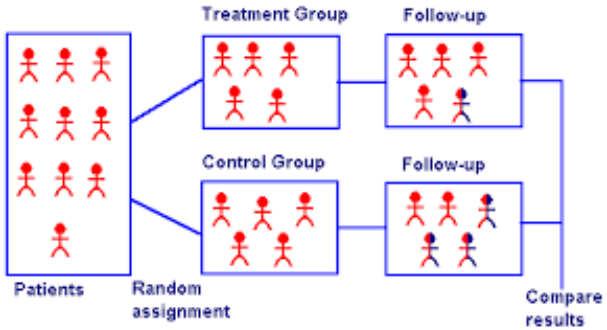


Medical Research Council (MRC) in the UK conducted the first double-blind clinical trial

1943

1946

MRC performed the first randomised clinical trial



Nuremberg Code made informed consent mandatory for all clinical trial participants

1947

1962

Kefauver-Harris Amendment added to the Food and Drug Cosmetic Act making randomised controlled, double blind clinical trials mandatory for the approval of new pharmaceuticals

ICH harmonisation for better health

ICH-GCP published - setting out a tripartite standard for the conduct of clinical trials across the EU, Japan and the US to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions

1996

1.4 ICH GCP guideline

The ICH GCP guideline published in 1996, is a consolidated document setting out a tripartite standard for the conduct of clinical trials across the European Union (EU), Japan and the United States (US)(11). The guideline were developed by drug regulators and the pharmaceutical industry in the early 1990s, with little input from academic researchers (92, 93). The aim of the guideline was to facilitate the standardization of clinical trial processes; so that clinical trial results would be accepted by regulatory authorities in these jurisdictions (11, 92). This means, for example that the results of a US based clinical trial conducted in accordance ICH GCP, can be accepted by the European Medicines Agency (EMA), the body responsible for drug licensing in Europe(94).

ICH GCP was finalised in 1996 and became effective in 1997 but was not enforced into law at this time (94, 95). The guideline quickly became an international ethical and scientific quality standard for the design, implementation, monitoring, recording, analyses and reporting of clinical trials that involve the participation of human subjects(11). It includes fourteen principles, that if followed should provide assurance that the data and reported results of a clinical trial are credible and accurate while still protecting the rights and safety of trial participants (Table 3)(23).

Table 3: ICH GCP principles

1	Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2	Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3	The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4	The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5	Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6	A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
7	The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8	Everyone involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9	Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10	All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11	The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12	Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol
13	Systems with procedures that assure the quality of every aspect of the trial should be implemented.
14	Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

The 2004 European Clinical Trials Directive (CTD) 2001/20/EC as S.I. 190(2004) changed the process of clinical trials. This Directive made compliance with the GCP guideline a legal requirement for all Clinical Trial of an Investigational Medicinal

Product (CTIMPs), conducted in Europe. CTIMPs examine the safety or efficacy of a medicine/foodstuff/placebo in humans (57).

The Directive aimed to regulate clinical research in a uniform way across Europe. It sought to speed up the research and development of new medicines by cutting the bureaucracy that was caused by differing regulatory requirements in different EU countries(57, 95, 96). To transpose the Directive into national law, each EU member including Ireland had to change its established legal framework for clinical drug research to meet the requirements of the Directive(95). Accordingly, in Ireland the new Directive superseded the Control of Clinical Trials Acts 1987 and 1990(97). Under the Directive clinical trials in Ireland, like in all EU countries, could only commence once the sponsor has received ethical and regulatory approval(98). In Ireland, approval to conduct a CTIMP must be granted by the Health Products Regulatory Authority (HPRA) and by an Ethics Committee which is supervised by the Department of Health and independent of pharmaceutical industry involvement(99). The HPRA and an Ethics Committee individually review a clinical trial application, containing supporting medical and scientific data primarily of laboratory and animal testing for toxicity(99). Once approval has been received from the HPRA and an Ethics Committee, a clinical trial must then be carried out in accordance with the EU Clinical Trial Directive and the ICH GCP guideline (97, 99).

1.4.1 Clinical Trial Monitoring

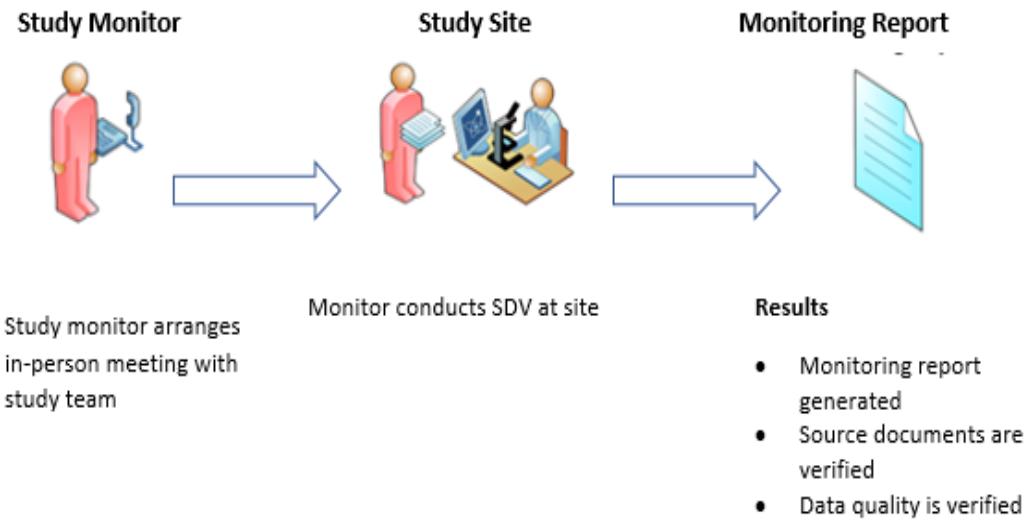
In accordance with the GCP guideline, enforced by legislation such as the EU Clinical Trial Directive, the clinical trial sponsor whether pharmaceutical, academic or a government agency, must set up appropriate measures to monitor their clinical trial(11, 57). Accordingly, monitoring should ensure the participants' wellbeing and safety is protected, that the trial complies with the approved protocol and regulatory requirements and that trial data are accurate and complete(11). GCP states that the sponsor must decide the appropriate type and frequency of monitoring required to adequately monitor their clinical trial(11). This decision should be based on the characteristics of the clinical trial such as its objective, phase, complexity, blinding, size, and endpoints under investigation(11). However regardless of the characterises

of a trial, the original ICH GCP guideline recommended on-site monitoring to be performed, before, during, and after the trial(11).

Traditionally, sponsors interpreted GCP's monitoring directive as a requirement for all clinical trials to be monitored through extensive on-site monitoring during which 100% source data verification (SDV) had to be performed on trial documents(100). This meant that all clinical trials regardless of the phase of the study, the investigational medicinal product under investigation, the study population or the experience of the individuals conducting the study; were monitored using the same traditional approach(100, 101). Even though, traditional monitoring can be time consuming and expensive to perform (100, 102).

On-site monitoring involves an in-person evaluation carried out by a study monitor at the clinical trial site location (Figure 1) (103, 104). During an on-site visit, source data verification is the process by which data, within a participant's case report form (CRF) or other data collection system, are compared to the original source of information(100).Normally, during an on-site visits, all the information documented in a participant's case report form is verified against source data such as hospital records, clinical and office charts, laboratory notes and pharmacy dispensing records(102, 105). This process, known as on-site SDV monitoring, aims to identify errors in case report forms, review essential documentation, assess protocol compliance and evaluate investigators supervision. The frequency of on-site visits in a clinical trial generally follows a pre-specified schedule that can be influenced by participant recruitment rates(106).

Figure 1: Traditional monitoring



A report published in 2014, estimated the cost of developing a prescription drug that gains market approval was $2.6 billion, a 145% increase since 2003 estimates(107), with the top three cost drivers of clinical trial expenditures being procedure costs, staff costs, and site monitoring costs (15%)(18, 108). Traditional monitoring has been criticized as being reactive, expensive and limited in its ability to quickly identify issues and prevent them from recurring(18, 100). Since monitoring a clinical trial by a monitor being physically being present, is expensive both in terms of money spent on logistics as well as time spent by a monitor attending each site(109). It is reported that almost 46% of on-site monitoring effort goes into SDV, which translates to about 34% of a total phase III study budget(110).

Although monitoring can consumed almost 15% of a clinical trial budget, evidence to support the effectiveness of on-site monitoring or SDV is lacking(111). In 2013, a systematic review of on-site monitoring, found methods differed worldwide with little evidence to suggest it guarantees participants' safety or prevents data quality issues(100). This may be due to SDV's limited ability to quickly identify issues such as incorrect participant consent procedures and prevent them from recurring in a clinical trial(18). Therefore, traditional on-site 100% SDV monitoring may be over cautious at best, and, at worst, might be a complete waste of resources(18, 100).

It must also be noted that the GCP guideline and consequently the EU Clinical Trial Directive does not stipulate upper and lower limits of on-site monitoring and source date verification(57). It has been suggested that the use of on-site visits and 100% source data verification was driven partly by concerns over the expectations of competent authorities such as the HPRA and in part by Contract Research Organization, who had a strong financial incentive to push 100% on-site source data verification(110).

Several reports recommend reducing on-site monitoring and replacing it with centralized monitoring (18, 20, 21). Centralized monitoring is the remote evaluation of the study data, carried out by monitors and clinical trial staff at a location other than the sites at which the clinical investigation is being conducted(112). A study conducted in 2012 found that more than 90% of the problems identified during on-site monitoring of a 9385 participant, 6-site trial performed in Africa, could have been identified by central monitoring practices(20). Furthermore, it is estimated that implementing a modified monitoring plan that largely replaces on-site monitoring with centralized monitoring could reduce clinical trial costs by more than 20%(18).

1.4.1.1 Centralized monitoring

Centralised monitoring allows monitoring activities which were previously conducted on-site to be conducted remotely(20). In centralized monitoring, the monitor is still very much involved, but he/she does not spend time onsite. Instead the monitor performs all the study monitoring processes remotely, using a secure online platform (20, 113). For example, in trial that perform centralized monitoring, the research team enter study and patient data into a database or paper forms(113). Once this is done, the research team have additional step of uploading all or some of the source documents, labs, medical histories, informed consent forms, and other such documents to the secured online platform which will then become available to the monitor instantaneously. This step may involve scanning documents to the online platform. Once the documents for a particular visit or referring to a specific clinical trial requirement (i.e. insurance certification) are on the online platform, the monitor can examine the documents for errors. The monitor then communicates the results

back to the clinical trial team via the online platform, email or telephone conversation(113).

However, for the purpose of this study, centralised monitoring will be defined as the remote monitoring of clinical trial data that is held on an Electronic Data Capture (EDC) system and not just the review of data from a remote location distant to the clinical trial investigation site (106, 107). This type of centralized monitoring has been described as a requirement for RBM(26). It has emerged from the need to speed up the progress of clinical trials to shorten research cycle and reduce the rate of data errors (20, 114). It involves a review of centralized data held on an Electronic Data Capture (EDC) system and not just the review of data from a remote location distant to the clinical trial investigation site(115, 116).

Conventional data collection for clinical trials involved collecting data on paper-based case report forms (CRF) followed by double data entry into an interactive data base(100). Although well established, this method was time consuming, resource heavy and prone to errors (92). It created substantial administration and cost implications as paper CRFs had to be couriered to a central data entry location, which introduced the risks of losing data, breaching data protection laws and damaging paper CRFs making them illegible(117). Moreover, this process slowed down the reporting and analyses of clinical trial results as a database could only be locked once all the paper-based data was validated and entered into the database(118).

In 1990, clinical researchers acted to alleviate the problems associated with paper based CRFs by changing to a remote data entry system(118). This system facilitated the submission of paper-based CRFs to the data center by fax. Then once received by the central data center, a data manager would manually type the information contained on the paper CRF into the central database(118). The development of modern technology networks, web based clinical data collection systems such as EDC systems, enabled clinical researchers to input data directly into the computer system (116, 117). This process also improved clinical trial monitoring as it allowed the monitor to log into the computer system and perform source data verification(119).

In addition, the EDC system had inbuilt programme edit checks that validated data entry in real time(118).

The increased use of EDC systems over the past decade have facilitated the use of centralized monitoring in clinical trials(119). These systems provide researchers with the capabilities to enter, review, analyses and edit data in real time and to implement online data validation checks to ensure improved data quality at the point of data entry(120, 121). In May 1997, the FDA issued the regulation 21 CRF Part 11, which provided guideline on EDCs and the use of electronic signatures(122). Under this regulation, EDCs are not classified as a computer system in clinical trial data management which is fully compliant with CRF 11(122). In 2018, it was estimated that more than 50% of clinical trials in the United States use an EDC system(116). The increased use of EDC systems has facilitated the use of centralised monitoring(116).

1.4.2 Problems with ICH GCP

By the early 2000s, despite the extensive global use of the ICH GCP guideline, researchers still questioned its value(123). Some researchers believed the ICH GCP guideline made clinical trials more expensive and complex to conduct(124). They believed the one-size fits all approach to the design and conduct of a clinical trial, taken by the ICH GCP guideline, was not appropriate(123). This is true as all clinical trials are not comparable; they vary greatly in terms of study populations, IMPs and research teams(40, 123). Many critics believe the ICH GCP guideline was developed for pharmaceutical companies conducting large, heavily resourced clinical trials and that ICH GCP was not tailored towards small clinical trials sponsored by academic institutions and individuals(123).

Members of the global clinical trial community thought the GCP guideline included an over emphasis on less important aspects of a clinical trial such as source data verification, at the expense of other important aspects of the clinical trial such a randomisation(124). Moreover, they believed that a lack of flexibility on the GCP guideline and its interpretation for low risk academic trials has resulted in clinical trial processes that are unnecessarily complex and expensive for low risk academic trials(92). This shortcoming is thought to have hindered the development and

adoption of innovative clinical trial methodologies in areas such as participant recruitment and the participant consent process(17, 92).

Since the GCP guideline was transposed into law with the introduction of the EU Clinical trial Directive in 2004, academic researchers have called for the guideline to be revised (123). Unlike other countries such as the USA and Japan, the EU Clinical Trial Directive did not differentiate between commercial and non-commercial academic trials(37). This means that the same level of regulation applies to all types of CTIMPs regardless of their risk profile. This results in making some trials such as Phase III trials of licenced drugs, excessively resource and time consuming without any benefit for the safety of the participants or the quality of the data(124).

In 2016, the More Trials initiative was established, by over 230 trialists from 35 countries, to instigate change to ICH GCP(124). The initiative called for aspects of clinical trials such as monitoring to be proportionate to the risks of the trial, which they believe is mostly dependent on the study drug under investigation(124). They state that a new drug in development would require much more intensive monitoring and safety review compared to a vitamin or over-the-counter product which has been in use for many years(124). One of More Trials suggestions, particularly in the context of academic sponsored, noncommercial trials is that monitoring should be tailored to the risk profile of each trial(124). A proportional approach to the ICH GCP guideline should be adapted to participant safety risks as well as to the risks related to the reliability of the trial results(25).

More Trial's request for a review of the ICH GCP guideline was answered in 2017 when ICH publicly recognised the failings of the ICH GCP guideline ;*"Although ICH E6 generally can be interpreted as providing sponsors flexibility to implement innovative approaches, it has been misinterpreted and implemented in ways that impede innovation by, for example, emphasizing less important aspects of trials (e.g., focusing on the completeness and accuracy of every piece of data) at the expense of critical aspects (e.g., carefully managing risks to the integrity of key outcome data)(125)."*

The ICH have recognised that when they first published ICH GCP guideline in 1996, the process of conducting a clinical trial, including risk assessment and monitoring, was largely paper-based(126). Since then clinical trials have advanced and they are now more complex, costly, large global projects. At the same time, major advances in technology and data analytics are making it possible for clinical trials to be more effective and efficient at certain aspects of monitoring such as centralised monitoring(127). To keep up with these advances, in 2017 the ICH published the International Council for Harmonisation (ICH) E6 – good clinical practice (GCP) (R2)(126). The aim of the revised ICH GPC guideline is to encourage the implementation of improved approaches for the management of clinical trials (127).

The change to ICH GCP comes from the clear recognition to have an open dialogue with all clinical trial stakeholders not just the pharmaceutical industry(125). By far the most substantial change to ICH E6 relates to clinical trial monitoring(23). Each study is now required to have a study-specific monitoring plan which was not a requirement in the original 1996 ICH GCP guideline(23). The monitoring plan should clearly state how and why the trial is to be monitored, taking consideration for the participant's safety and data integrity. In addition, the revised ICH GCP guideline, per section 5.18 requires the sponsor to develop 'monitoring reports', including both centralised reports and on-site monitoring visit reports and now these reports must be provided to the sponsors by the monitor in a timely manner and with enough detail to allow sponsors to follow up, if needed(23). Finally, the addendum incorporates elements from the FDA's (2013) risk-based monitoring guidance, which supports alternative monitoring approaches such as risk-based monitoring to traditional extensive on-site monitoring with 100% SDV(12, 23).

1.5 Transition to Risk based monitoring – ICH GCP E6 R2

Globally, clinical researchers are looking for ways to reduce the cost and increase the quality of clinical trial monitoring(23). Risk based monitoring (RBM) has been proposed as one such solution (23, 128, 129). The RBM approach as endorsed by the new ICH GCP guideline has several main objectives. First, it is intended to enable more real-time identification of emerging trends and potential risks that impact patient safety and data integrity(10). Secondly this risk-proportionate approach is

intended to enable monitors, when on-site, to focus more on the activities that best support the site and drive data quality and patient safety(10). The new ICH GCP guideline echoes FDA's endorsement of RBM which recommends that sponsors develop a systematic, prioritized, risk-based approach to monitoring clinical trials(12, 23). This approach should include a combination of on-site and centralised monitoring, or, where justified just centralised monitoring alone(23). The sponsor should document the rationale for the chosen monitoring strategy in the monitoring plan(23).

To achieve these objectives, RBM should incorporate both on-site and centralised monitoring that are proportional to the risks associated with the clinical trial(10). These risks relate to the IMP, study population and the robustness of the study design(26). RBM should enable clinical researchers to focus on all aspects of a clinical trial from protocol development to data analysis (127). It should allow researchers to be flexible and adjustable to unexpected risks that emerge along the duration of a clinical trial. Ideally, the RBM process should start at the time of protocol design, so mitigation can be built into the protocol and other trial related documents (e.g. monitoring plan) (26). Moreover once a trial starts, RBM should become a pre-emptive process and so the risk profile of a trial should be continuously reviewed and monitoring practices modified accordingly (26). By focusing on clinical trial risks, it is thought the implementation of RBM should improve clinical trial data quality while ensuring subjects' rights protection and regulatory compliance(128).

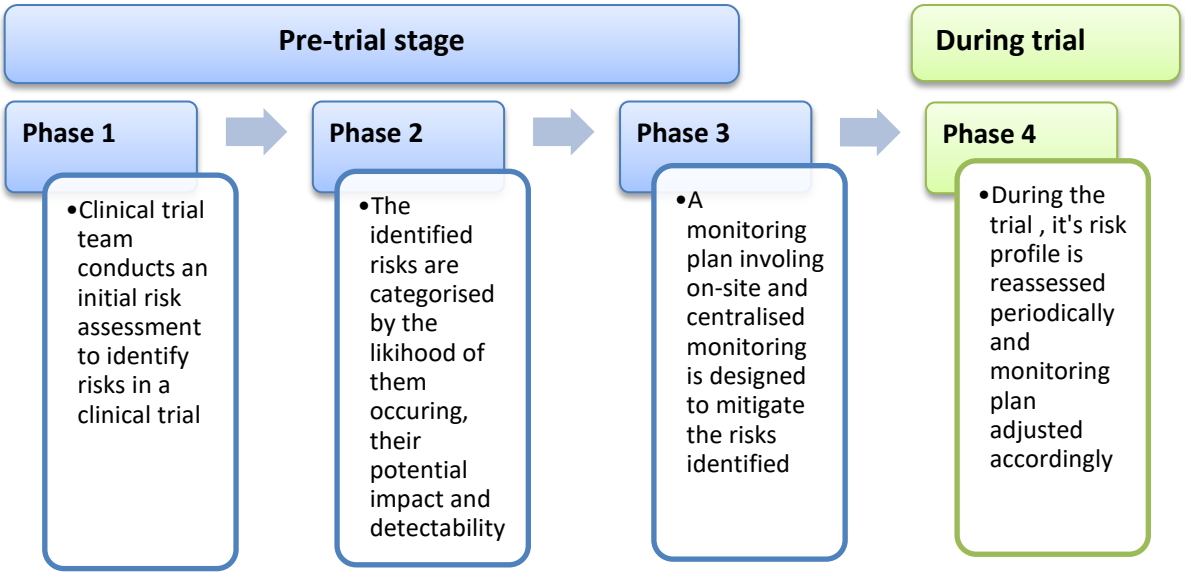
1.5.1 RBM process

The new ICH GCP guideline sets a target for RBM, but does not describe a path towards implementation(130). Indeed, RBM cannot be served by a "one size fits all" approach and ICH's acknowledgement is welcomed regarding the sponsor's responsibility to determine the optimal approach to study oversight and not mandate any given strategy(28). However, as stated above, the new ICH GCP guideline suggests RBM should involve a combination of onsite and centralized monitoring activities(23). Unfortunately, the guideline fails to provide more detail or

instruction related to how a sponsor can determine to what extent this combination of on-site and centralised monitoring is right for their clinical trial (25).

However, several more specific recommendations for RBM do exist(10, 26). For example in 2012 a group of biopharmaceutical companies called TransCelerate developed a four stage RBM approach outlined in Figure 2 (26). .This approach first involves a risk assessment to identify clinical trial risks that could affect participants' safety or clinical trial data(26). Such risks relate to the complexity of the study design, the study population, study team's experience, the safety profile of the IMP and the quantity of data been collected(26). The identified risks should then be assessed and prioritized by considering the likelihood of errors occurring, impact of such errors on participants protection and trial integrity and the extent to which such errors would be detectable(26). Secondly, the results of the risk assessment should guide the development of a monitoring plan(26). The type (e.g., on-site or centralized), frequency (e.g., early versus throughout the study), and extent (100% SDV versus targeted or random review of certain data), of monitoring activities should depend on the frequency and types of risks identified during the risk assessment(26). Finally, once a trial starts, RBM should become a pre-emptive process(26). Sponsors must continuously review the risk profile of a trial while it is ongoing and modify monitoring practices accordingly(26). When done correctly, it is suggested that RBM can allow for the proactive mitigation of likely sources of error, rather than the reactive correction of errors that have already happened(131).

Figure 2: RBM process



Furthermore in 2012, the Organisation for Economic Co-operation and Development (OECD) published recommendations for clinical trial governance which advised clinical researchers to use a RBM tool when developing their RBM plan(10). Such tools have two functions, first they must support the assessment of risk in a clinical trial protocol and secondly that should provide guidance for subsequent monitoring activity that can mitigate the risks identified(10, 27). For example, TransCelerate's Risk Assessment and Categorization Tool (RACT) is a RBM tool that helps determine risks that could affect subject safety, data quality and regulatory compliance, and provides guidance on how and by which function the risks may be managed(112). A variety of paper based and electronic RBM tools have been developed but, to date, research comparing them has not been conducted(132).

For RBM to be efficient, it is imperative that the initial risk assessment phase is simple and does not create additional burden for a clinical trial team (27). However despite the availability of RBM guidance, the question remains around how clinical trial risk should be measured(32).Various RBM strategies for clinical trials have been developed across the world, particularly with the objective of defining clinical trial risk(32). These include:

1. Stratified approach -based on the definition of discrete risk categories.

This approach involves determining the risk profile of a clinical trial based on the market authorization of the Investigational Medicinal Product under investigation (28). This process will lead a discrete single dimension of risk based solely on the hazards to participants related to the study drug(28). This approach has inspired a UK initiative that created three risk categories based on the IMP(28):

- **Category A:** Clinical trials using already marketed medicine under the licensed indication
- **Category B:** Clinical trials using already marketed medicinal products, exploring their use in new indications, new populations
- **Categories C:** Clinical trials exploring safety and efficacy of never marketed medicinal products

This process is limited as it does not take account of other risk factors in a trial such as study population and experience of the study team(28, 133). It is suggested that a stratified approach to risk assessment will result in a monitoring strategy that will only mitigate the risks imposed by the marketing status of the Investigational Medicinal Product(28).

2. Personalized approach -based on a case per case assessment of each individual clinical trial protocol using guidance and decision trees.

The personalized approach involves an individual unique risk assessment and risk mitigation strategy for every clinical trial(32). This risk assessment process is conducted on a case by case basis, to assess all the risks associated with an individual trial prior to the trial starting and the monitor's green light visit(134). This approach is supported by decision trees and taxonomy such as the Risk indicator taxonomy for supervision of clinical trials on medicinal products(133).

The personalized risk assessment approach considers the various dimensions of predefined clinical trial risks such as: hazards to the participants (rights, safety) and hazards to the results data design and analysis). It also considers the experience and training of the trial team, as well as the robustness of trial procedures such as

randomization and determinants of data credibility(32). The personalized approach aligns to the quality by design concept which states that a clinical trial monitoring plan should focus on critical points of the trial protocol(32).

1.6 RBM evidence gap

The new ICH GCP guideline has truly brought RBM to the forefront of clinical trial monitoring(25). However, for monitoring to become truly risk-based there needs to be cultural shift in many clinical trial teams(29). The concept of RBM implies that the chosen monitoring strategy is adapted to the local and trial-specific context(135). This means that a one-size-fits-all model is not possible(130). However, despite the availability of RBM guidelines, challenges still exist with respect to clinical researchers establishing a local RBM process and implementing it in the desired way(29, 135). A survey of Clinical Research Organizations found the biggest challenges with implementing RBM are a lack of internal knowledge/expertise, perceived inability to maintain sufficient quality through RBM and lack of capacity to rapidly adapt to changing RBM needs(129). Similarly, a US based report found sponsors were reluctant to try new quality control methods such as RBM because they felt they would increase their risk of failing an FDA audit(18). These concerns are not without merit, and, to date, no gold standard RBM approach has been developed (129).

In anticipation of the ICH GCP Addendum industry sponsors, such as CROs and pharmaceutical companies that conduct commercial clinical trials, published opinion pieces and white papers describing how RBM should be implemented and barriers to its implementation(136). Many of these papers view RBM as the same process as centralised monitoring, meaning that RBM must be conducted without using centralised monitoring activity(137). Furthermore it appears centralised monitoring is the biggest driver for RBM by industry sponsors. Many of the papers claim that RBM which is performed through centralised monitoring is cheaper, less resource-intensive and, more efficient than traditional on-site monitoring(137, 138).

The industry sponsors (CROs and pharmaceutical companies) like academic sponsors claim that the successful implementation of RBM from pilot studies to full-scale rollout requires a foundation of quality, appropriate processes, and analytics(139).

Industry is acknowledging the realignment of processes and roles, and adoption of software technologies that require serious consideration when organizations consider implementing RBM(136, 139). Industry sponsors are looking for electronic software providers and tools to support them to perform RBM through centralised monitoring, through the provision of services that can predict key risk indicators in their clinical trials that will subsequently inform their RBM plan (138, 139).

The implementation of RBM, with the consequent adjustment or reduction of onsite monitoring visits and source data verification (SDV), can only succeed after establishing an appropriate RBM approach(10, 140). The way that risks are identified, evaluated and mitigated commands a change in the mind-set of those who have applied ICH GCP and traditional 100% on-site monitoring since 1996(110, 141). Given the complexity of risk assessment in clinical trials, appropriate training for clinical researchers are yet to be developed to ensure both the reliability of the assessment and the development of effective RBM plans(10). Considering that the rationale of the chosen monitoring strategy should be documented, the ICH assumes that every sponsor would know the advantages of one monitoring method (on-site or centralised) over the other and will be able to choose the right levels of application of these methods in their clinical trial (141). Thus to develop an effective RBM plan, a clinical trial team should know and understand the rationale for use of the chosen RBM method(110).

The assumption that RBM reduces waste of valuable clinical trial resources, such as study budget and staff time and improves participant safety or data quality has yet to be proven(31, 129). For example, studies such as the Risk ADApted MONitoring (ADAMON) and the OPTimisation of MONitoring for clinical research studies (OPTIMON) projects evaluating the effectiveness and cost efficiency of RBM are still ongoing or have produced little evidence to suggest RBM is more effective that 100% on-site monitoring (Table 4)(129, 142). Therefore it is imperative with RBM, that the monitoring approach should not exempt the sponsor or investigator from their responsibilities, and that even if the trial is considered ‘low risk’ participant safety must not be neglected(141).

Table 4: RBM research

Study	Aim	Results
Risk ADApted MONitoring (ADAMON) project	Investigate whether a RBM strategy developed by a RBM tool was equivalent to an extensive full monitoring approach	Published 2017: RBM offers potential benefit over extensive on-site monitoring(142)
OPTimisation of MONitoring for clinical research studies (OPTIMON)	Compare the efficacy of two monitoring strategies: one based on the classic standards of quality assurance, and the other one being a priori optimised strategy guided by an RBM tool	Released in 2015: OPTIMON lacked sufficient statistical power to demonstrate non-inferiority of the RBM approach at detecting severe errors(143)
START Monitoring Sub study (or SMS)	Evaluate and compare data monitoring with two vs three components: (central +local monitoring) compared to (central + local + on-site monitoring)	Not published(144)
Targeted Monitoring, Prospective Evaluation and Refine Study (TEMPER)	Evaluate targeted monitoring within several multicenter cancer trials being conducted by the MRC Clinical Trials Unit. Using a pre-specified trigger for each trial, sites prioritized for a site visit will be matched (on number of patients recruited and time since trial site opened) with one that would not be visited based on the normal monitoring strategy	Published in 2018: Triggered monitoring approaches, as used in these trials, were not sufficiently discriminatory(113)

1.7 RBM – implementation in Irish academic-led clinical trials

Since 2011, health regulators such as the FDA, EMA, the Medicines and Healthcare Products Regulatory Agency (MHRA), the Japan Ministry of Health and Swiss Federal Constitution have driven initiatives to transition clinical trial monitoring to RBM in their local clinical trial organisations (12, 24, 28, 145). For example in 2013, the FDA released a clinical trial guidance document that approved RBM as the preferred method for trial monitoring (12). In 2014, Switzerland became the first European country to introduce a a regulation adopting risk-based categorization into their clinical trial methodology(146).

In contrast, Ireland's Health Products Regulatory Authority (HPRA) have not published RBM guidance. Similarly, the Health Research Board-Clinical Research Coordination Ireland (HRB-CRCI) does not have a national strategy to support the introduction of RBM into its publicly funded, academic run clinical trial units. In the absence of a gold standard RBM approach and national RBM guidelines it remains unclear how Irish sponsors will translate ICH GCP's RBM directive into practice in their clinical trials. This is a cause for concern, as clinical trials in Ireland are legally obliged to operate in accordance with GCP guideline and in doing so they must perform RBM(99).

1.8 Thesis Aim

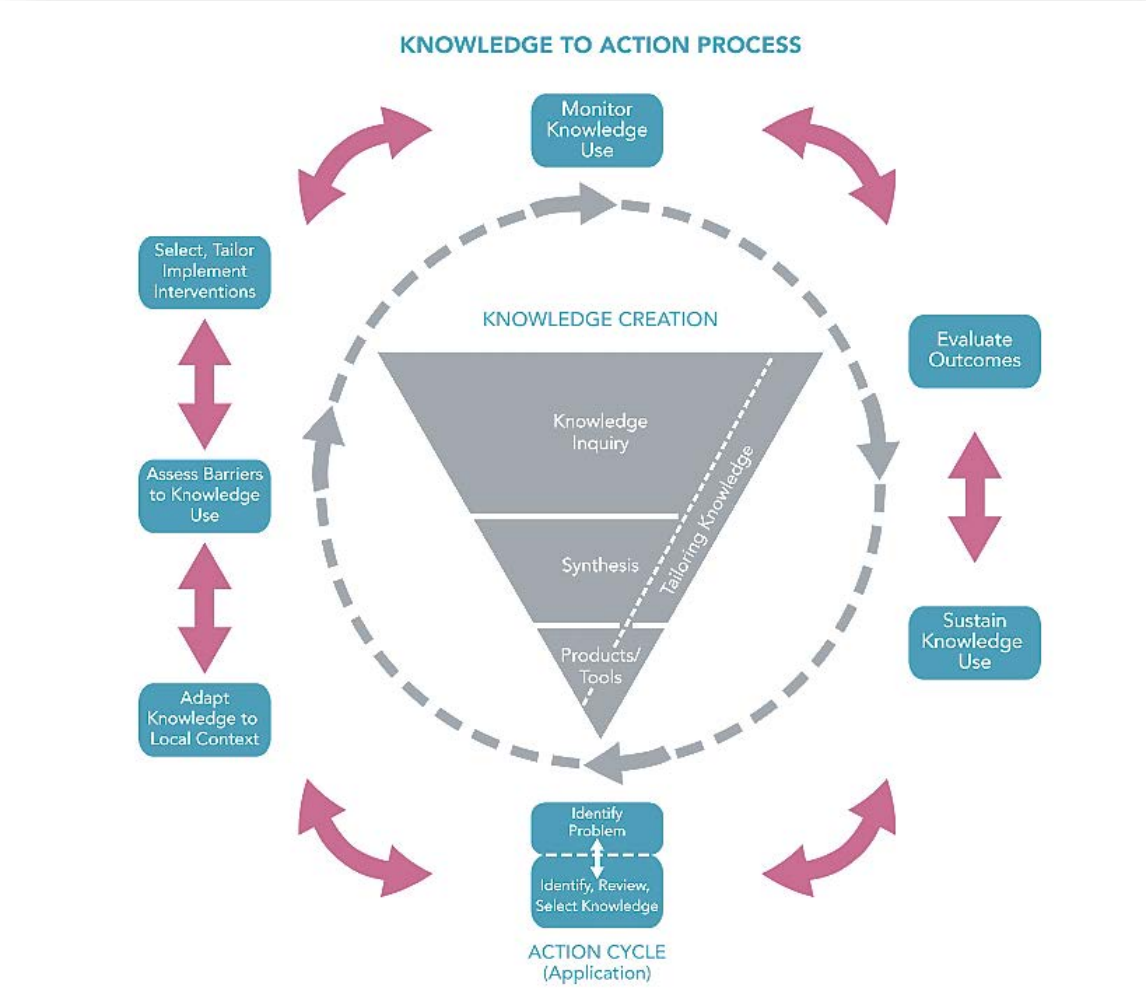
This thesis aims to develop, implement and evaluate a quality improvement (QI) intervention to support the implementation of RBM into academic-led clinical trials in Ireland. To date QI interventions have led to changes that have produced better patient outcomes, better system performance and better professional development(147). However, there is a paucity of evidence documenting the value of QI in the conduct of clinical trials to promote high quality and efficient clinical trials(148). This thesis supports the global initiative aimed at increasing QI use in clinical trials to improve clinical trial methodology (148-150).

The thesis follows the Knowledge to Action framework which is a conceptual framework intended to help deliver sustainable, evidence-based knowledge translation interventions(151). Knowledge Translation encompasses all steps

between the creation of new knowledge and its application to yield beneficial outcomes for the knowledge user, who is an individual likely to use research results to make informed decisions about health policies, programs and/or practices(152, 153). For the purposes of this thesis, the knowledge users are clinical researchers working in the CRF/Cs affiliated with the HRB-CRCI in Ireland(64). They include principle investigators (PIs), pharmacists, study physicians, nurses, project and quality managers, study monitors and statisticians(64).

The Knowledge to Action Framework (outlined in Figure 3) has two distinct but related components: (I) Knowledge Creation (represented by the funnel) surrounded by (ii) the Action Cycle which outlines a process, representing the activities needed for knowledge to be applied in practice; knowledge is adapted to the local context, and barriers and facilitators to its use are explicitly assessed(151). The Knowledge to Action phases can be carried out sequentially or simultaneously and the knowledge phases may impact on the action phases(151). However at each stage of the Knowledge to Action process, the information generated or action taken must be tailored to the knowledge user(151).

Figure 3: Knowledge to Action framework



1.8.1 Thesis Objectives

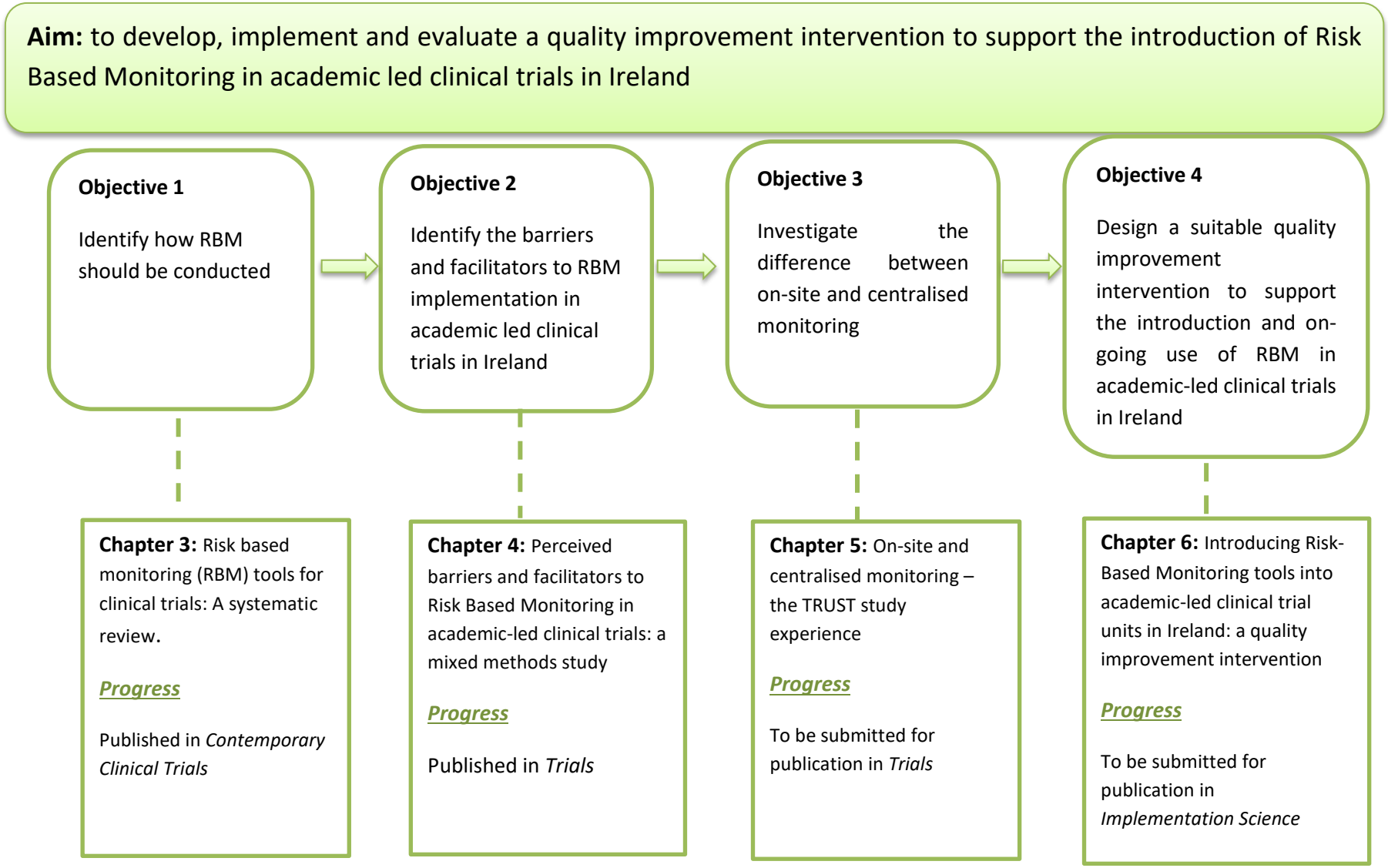
The specific objectives of the thesis are informed by the core components of the Knowledge to Action framework which are knowledge creation and the application of this knowledge into practice. To fulfil the components of the Knowledge to Action framework, this thesis will address the following four objectives:

1. Identify how RBM should be conducted.
2. Identify the barriers and facilitators to RBM implementation in academic led clinical trials in Ireland.
3. Investigate the difference between on-site and centralized monitoring.
4. Design a suitable quality improvement intervention to support the introduction and on-going use of RBM in academic-led clinical trials in Ireland.

1.9 Chapter Outline

This thesis has seven chapters including the Introduction. Chapter 2 describes the overall thesis methodology. Chapters 3, 4, 5 and 6 consist of manuscripts that each fulfil one of the four thesis objectives outlined above (Figure 4). Lastly, Chapter 7 summaries and compares the findings from those four manuscripts, contextualize the findings within the existing literature, and identifies contributions and direction for future research.

Figure 4: Thesis outline



Chapter 2. Methods

2.1 Introduction

This thesis aims to develop, implement and evaluate a quality improvement intervention to support the implementation of RBM into academic-led clinical trials in Ireland. To achieve this aim, a multi-method research strategy, informed by the Knowledge to Action framework was employed. Several Knowledge Translation frameworks exist(154). To select a suitable Knowledge Translation framework for this thesis, a search of PubMed and Google Scholar was conducted in 2014 and ten potential Knowledge Translation frameworks were identified (Appendix A). The Knowledge to Action framework was identified as the most appropriate for this research project because it best supported the aim of this thesis.

This chapter outlines the phased implementation of the Knowledge to Action framework which was executed through a multi-method research strategy over four years from October 2014. Multi-method research involves the combination of individual research elements to provide an answer to one research question (1). It is not the same as mixed methods research, which incorporates various quantitative and qualitative strategies in a single research project (1).

2.1.1 Knowledge to Action framework

The Knowledge to Action framework has two components (i) Knowledge Creation and (ii) the Action Cycle, which has seven subcomponents:

1. identifying research problems and selecting knowledge
2. adapting knowledge to local context
3. accessing barriers to knowledge use
4. selecting, tailoring and implementing intervention
5. monitoring knowledge use
6. evaluating outcome
7. sustaining on-going knowledge use (2).

Accordingly, this thesis included four individual pieces of research that were guided by the components of the knowledge to Action framework (Table 5). For example, this meant that at least one of the research elements had to create RBM knowledge, as knowledge creation is a core component of the Knowledge to Action framework(151).

Table 5: Application of the Knowledge to Action framework

Study	Knowledge to Action component	Objective	Study design
1	**Knowledge creation**	Examine how should RBM be implemented	Systematic review
2	**Action Cycle** • Identify problems and select knowledge • Adapt knowledge to local context • Assess barriers to knowledge use	Identify the barriers and facilitator to RBM implementation in academic-led clinical trials in Ireland?	Mixed methods- quantitative & qualitative
3	**Knowledge creation**	Investigate the difference between on-site and centralised monitoring	Document analysis
4	**Action cycle** • Select, tailor and implement intervention • Monitor knowledge use • Evaluate outcome • Sustain on-going knowledge use	Identify a suitable knowledge translation strategy to support the introduction and on-going use of RBM in academic-led clinical trials in Ireland	Quality Improvement (QI) study

2.2 Data collection process

The research for this thesis was done in four phases. The aim and methodology of each of the separate four research phases were developed using an emergent

approach such that the results of one study informed the development of the subsequent study. Each phase is summarized below and described in detail in the following chapters.

2.2.1 Phase 1: Knowledge creation

Phase one involved the creation of RBM knowledge through a systematic review of RBM tools. The full title of the systematic review is *'Risk based monitoring (RBM) tools for clinical trials: A systematic review'* (3). It is described in detail in Chapter 3.

When the thesis began in 2014, regulatory documents produced by the FDA and the EMA did not provide clear RBM guidance (12). At that time, RBM tools had been developed which provided structured, clear RBM guidance (3). As defined by the OECD, RBM tools provide instruction on how clinical researchers should assess the risks in their clinical trial protocol and recommend monitoring activity that could mitigate the risks identified (4). However, despite the availability of RBM tools, a gold standard approach did not exist and literature comparing the methodology used in each tool was lacking (3).

A systematic review was the most appropriate research method to identify and compare RBM tools as such a review facilitates the collection and comparison of all empirical evidence relating to a research question (5). For this reason, I conducted a systematic review to identify, characterize and compare RBM tools. (4, 6).

2.2.2 Phase 2 - Action cycle

Phase two of my thesis was based on the action cycle of the Knowledge to Action (Table 5). The aim of this phase was to complete the first, three subcomponents of the action cycle; which are to identify problems and select knowledge, adapt knowledge to local context and access barriers to knowledge use (2). To fulfill these criteria, I conducted a mixed methods study titled '*Perceived barriers and facilitators to Risk Based Monitoring in academic-led clinical trials: a mixed methods study'* (7). This phase is described in detail in Chapter 4.

In 2015, Ireland, unlike countries such as Switzerland and the UK, did not have a national strategy to support the introduction of RBM into its publicly funded,

academic-led clinical trial units (8, 9). The absence of a national strategy and gold standard RBM approach meant it was not clear how RBM would be implemented into their clinical trial units (7). Given this context, the aim of the mixed methods study was to establish how prepared academic trialists were to perform RBM (7). To achieve this aim, I explored the experience of, attitudes to, and perceived barriers and facilitators associated with the implementation of RBM in academic clinical trial units in Ireland (7). I decided to use a mixed methods approach as it allowed for the triangulation of quantitative and qualitative data that enabled an in-depth examination of my findings (10).

2.2.3 Phase 3 – Knowledge creation

The results of the Phase 2, mixed methods study, showed that academic clinical researchers in Ireland had limited experience of conducting centralised monitoring and felt less equipped to perform this type of monitoring compared to on-site monitoring. This primarily due to a lack of centralised monitoring guidelines and knowledge (7). This finding was consistent with literature in the area, which showed the limited nature of research describing and comparing the implementation of on-site and centralised monitoring in a clinical trial (12) To overcome this evidence gap and to create RBM knowledge, I conducted a Study Within a Trial (SWAT) to provide the first document analysis of on-site and centralised monitoring reports collected prospectively in a recent international multi-centre clinical trial: The TRUST Thyroid Trial (14, 15). This study, '*On-site versus centralised monitoring – the TRUST Thyroid Trial experience*', is described in detail in Chapter 5.

2.2.4 Phase 4 – Action cycle

The aim of Phase 4 was to complete the last, four subcomponents of the Action cycle. These are select, tailor and implement a Knowledge Translation intervention, monitor its use, evaluate its outcome and sustain on-going knowledge use (2). To fulfill these criteria, I conducted a quality improvement intervention study titled '*Introducing risk-based monitoring tools into academic-led clinical trial units in Ireland: a quality improvement intervention'.* This phase is described in detail in Chapter 6.

Phase 4 was informed by the results of my mixed methods study (Phase 2) and systematic review (Phase 1). The mixed method study had shown that a lack of RBM tool usage was one of the main barriers to RBM implementation in academic-led clinical trials in Ireland (7). This barrier was intensified by a lack of regulatory endorsed RBM guideline (7). To overcome this barrier, I decided to develop a quality improvement (QI) intervention that would support the use of RBM tools in academic CRF/Cs. Participants were clinical researchers recruited from academic-led CRF/Cs in Ireland.

2.3 Ethical considerations

Ethics approval was required for Phase 2 because it involved primary data collection from study participants. Accordingly, ethical approval was obtained from the Research Ethics Committee of the Cork Teaching Hospitals (CREC). Ethical approval was not required for Phase 1, 3 and 4 because Phase 1 and 3 involved secondary data analysis and Phase 4 was a Quality Improvement intervention which is exempt from the requirement for ethical approval (17). Ethical considerations are described in detail in Chapters 3, 4, 5 and 6.

2.4 Participants

Phase 2 and Phase 4 involved data collection from study participants which included principle investigators (PIs), pharmacists, study physicians, nurses, project and quality managers, study monitors and biostatisticians working in one of the five university led CRF/Cs in Ireland. Participants and the recruitment process are described in detail in Chapter 4 and Chapter 6.

Chapter 3. Risk based monitoring (RBM) tools for clinical trials: A systematic review.

Caroline Hurley

Frances Shiely

Jessica Power

Mike Clarke

Joseph Eustace

Evelyn Flanagan

Patricia Kearney

This paper was published in the journal of Contemporary Clinical Trials in 2016, please see Appendix H.

3.1 Abstract

Introduction: In November 2016, the Integrated Addendum to ICH-GCP E6 (R2) will advise trial sponsors to develop a risk-based approach to clinical trial monitoring. This new process is commonly known as risk-based monitoring (RBM). To date, a variety of tools have been developed to guide RBM. However, a gold standard approach does not exist. This review aims to identify and examine RBM tools.

Methods: Review of published and grey literature using a detailed search-strategy and cross-checking of reference lists. This review included academic and commercial instruments that met the Organisation for Economic Co-operation and Development's (OECD) classification of RBM tools.

Results: Ninety-one potential RBM tools were identified and 24 were eligible for inclusion. These tools were published between 2000 and 2015. Eight tools were paper based or electronic questionnaires and 16 operated as Service as a System (SaaS). Risk associated with the investigational medicinal product (IMP), phase of the clinical trial and study population were examined by all tools and suitable mitigation guidance through on-site and centralised monitoring was provided.

Conclusion: RBM tools for clinical trials are relatively new, their features and use vary widely, and they continue to evolve. This makes it difficult to identify the "best" RBM technique or tool. For example, equivalence testing is required to determine if RBM strategies directed by paper based and SaaS based RBM tools are comparable. Such research could be embedded within multi-centre clinical trials and conducted as a SWAT (Study within a Trial).

3.2 Introduction

The ICH-GCP guideline list clinical trial monitoring as a primary quality standard. Accordingly, trial sponsors must monitor their trial to ensure it complies with regulatory obligations, safeguards its participants and produces reliable data (11). More traditional monitoring approaches rely on intensive on-site visits and 100% source data verification (SDV) irrespective of the risk levels in the study(11, 22). SDV can be a laborious task because it involves the validation of data presented in case

report forms (CRFs) against original source data such as laboratory notes, pharmacy dispensing records and consent forms(11, 104). In recent years, SDV and on-site monitoring have been associated with high cost and limited contribution to clinical trial data quality (105, 155, 156). Consequently, those responsible for the ICH-GCP wish to reform clinical trial monitoring(12, 24). In June 2015, the ICH published a draft version of the integrated addendum to ICH-GCP, advising Sponsors to develop a systematic, prioritised, risk-based approach to monitoring clinical trials(157). This process is more commonly known as risk-based monitoring (RBM). It will also be prioritised in the forthcoming European Union (EU) Clinical Trial Regulation when reduced monitoring will be permitted for low-risk intervention trials(128). It is hypothesised that RBM will prevent valuable clinical trial resources, such as study budget and staff time, being wasted on unnecessary monitoring activity that does not improve participant safety or data quality (130, 156).

RBM incorporates both centralised monitoring conducted off-site through an examination of electronic trial data and on-site monitoring practices that are proportional to the risks associated with the clinical trial(12, 24). These risks relate to the Investigational Medicinal Product (IMP), the study population, research team and the robustness of the study design(133). For example, in high-risk trials RBM may involve 100% SDV onsite monitoring while for low-risk trials it may include 80% SDV through centralised and on-site monitoring practices(12, 24). Moreover, once a trial starts, RBM becomes a reactive process. Sponsors must continuously review the risk profile of a trial while it is ongoing and modify monitoring practices accordingly. The Organisation for Economic Co-operation and Development (OECD) advise clinical researchers to use a RBM tool when developing their RBM plan(10). Such tools should have two functions, firstly they must support the assessment of risk in a clinical trial protocol and secondly they should provide guidance for subsequent monitoring activity that can mitigate the risk identified(10). A variety of paper based and electronic RBM tools have been developed (129, 158). To date, research comparing them has not been conducted(10). The purpose of this review is to systematically identify and summarize RBM tools for clinical trial monitoring.

3.3 Methods

A descriptive narrative synthesis method was chosen for this review. This allows the findings of literature derived from qualitative and quantitative methods to be synthesised by identifying gaps, extracting data and grouping common ideas or arguments(159).

3.3.1 Ethical consideration

Ethical approval was not required for this study as no human subjects were involved and all data used in the review are available in the public domain.

3.3.2 Search strategy

PubMed and EMBASE were systematically searched for relevant published literature in August 2016 using a detailed search strategy (see Appendix B). No language or publication date restrictions were applied in the search or in the selection process.

In August 2016, the Google search engine was searched to identify eligible grey literature which was defined according to the Twelfth International Conference on Grey Literature's definition as follows:

> 'Grey literature stands for manifold document types produced on all levels of government, academics, business and industry in print and electronic formats that are protected by intellectual trial property rights, of sufficient quality to be collected and preserved by library holdings or institutional repositories, but not controlled by commercial publishers i.e., where publishing is not the primary activity of the producing body'(160).

The following search terms were used: *Clinical trial AND risk assessment tool OR risk analysis AND Risk based monitoring*. The Google search was restricted to the first 25 pages of results as no eligible papers were identified after the 16th page of results. No other restrictions were applied through the Google advanced search function. European experts, working on academic and commercially led clinical trials, were contacted by email and asked to name computer aided commercial RBM tools not identified during the search of published and grey literature. Publicly available

databases, ClinicalTrial.gov and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for supplementary documents(161, 162). In addition, the references in all eligible literature were checked for RBM tools that had not been identified by other means(163).

In total, 443 titles or abstracts of papers and documents describing RBM tools were retrieved from published and grey literature. Two independent reviewers, Caroline Hurley (CH) and Jessica Power (JP) assessed these documents for eligibility using the eligibility criteria listed below.

3.3.3 Inclusion criteria

- Peer-reviewed publications and grey literature as defined by the Twelfth International Conference on Grey Literature.
- RBM tools meeting the OECD criteria for such tools.
- RBM tools that were developed by academic, regulatory and commercial organisations such as Contract Research Organisations (CROs) that outsource clinical trial management for pharmaceutical, biotechnology and medical device industries and Independent Software Vendors (ISVs) that specialize in making or selling software designed for mass or niche markets(164).
- RBM tools for which information was available in the public domain or was provided to us to allow sufficient details about the tool to be included in this review.

3.3.4. Exclusion criteria

- Literature that only provided general narrative guidance for RBM in clinical trials and did not discuss RBM tools.
- RBM tools from commercial organisations (CROs and ISVs) that did not consent for their RBM tool to be included in this review (see Figure 6).

3.3.5. Quality assessment

CH assessed the methodological quality of included literature using the authority, accuracy, coverage, objectivity, date and significance (AACODS) checklist for grey

literature(165), which has been used in other research assessing the quality of grey literature(166-168). The AACODS checklist grades papers on a scale from of 0–6 (165). A paper was awarded a high-quality score if it fulfilled five or six of the following quality criteria; authority, accuracy, coverage, objectivity, date and significance (see Appendix B).

3.3.6 Data extraction

Two reviewers (CH and JP) extracted data from the eligible papers that described a tool specifically designed to guide RBM. The extracted data covered:

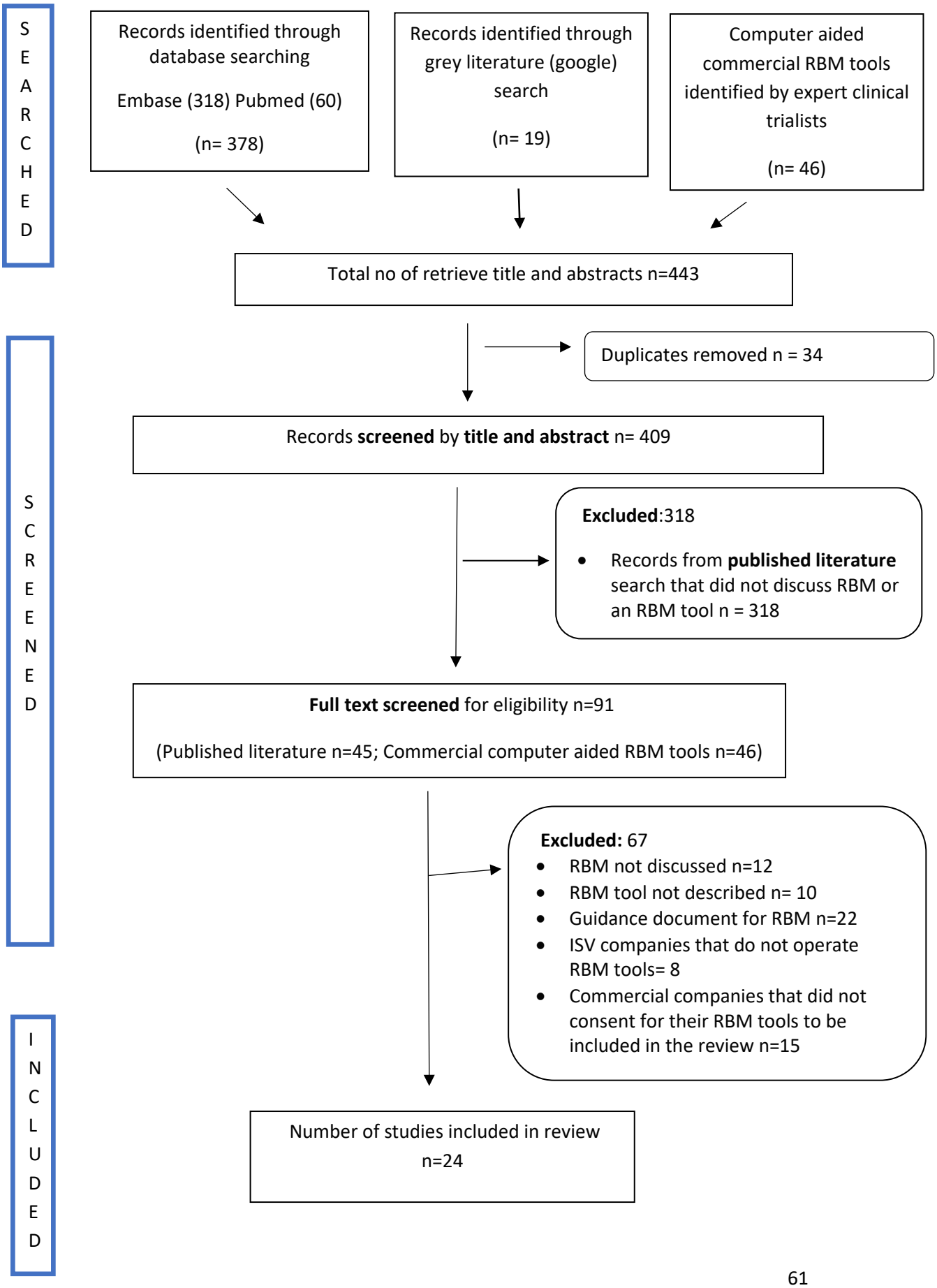
- Characteristics of the RBM tools – authors, geographical location, the tool's language and mode of administration etc.
- Risk indicators used by each tool to identify and classify risks in a clinical trial.
- Monitoring guidelines recommended by each tool to mitigate the risk identified.

3.4 Results

3.4.1 Search strategy

After initial screening of titles and abstracts, 91 papers or documents were eligible for further examination. Both reviewers (CH and JP) obtained the full text of these papers or documents and supplemental information on their corresponding RBM tools, through consultation with associated authors and commercial organisations (CROs and ISV). Twenty-four of these papers or documents and their corresponding RBM tools met the inclusion criteria and were included in the review. An overview of the literature review process is displayed in Figure 6, using the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram.

Figure 5: PRISMA flowchart



3.4.2. Risk assessment tools – characteristics

3.4.2.1 Affiliated clinical trial organisation; year of publication/release and country of origin

This review identified 24 eligible RBM tools and their characteristics are outlined in Table 6. Nineteen tools were sourced from grey literature and the other five tools were obtained from published papers. All the identified tools were published or released between 2000 and 2015 in Europe, the USA or Russia. All tools can be applied to all clinical trial phases (Phase I to Phase IV) and clinical trials of medical devices apart from the Risk classification method, Risk Assessment Tool (RAT) and the TORPEDO-CF: Risk analysis form(27, 169). Five RBM tools were developed by academic clinical trial researchers (Table 6: items1&4–7). Two RBM tools were developed by academic and regulatory organisations (Table 6: items 2–3). TransCelerate's Risk Assessment Categorization Tool (RACT) was the only tool in this review to be developed by a non-profit biopharmaceutical organisation (Table 6: item 8). The remaining 16 RBM tools were developed by commercial organisations, CROs and ISVs.

3.4.2.2 Mode of administration

Six of the RBM tools are paper based checklists (Table 6: items 1–5 and 7). Two tools, the Risk Assessment Categorization Tool (RACT) (26)and the SCTO risk assessment(170), function via Microsoft Excel. The other 16 RBM tools operate as commercial computer aided Service as a Systems (SaaS) that can be accessed through a web browser (Table 6: items 9–24). Three SaaS RBM tools; the Quality Risk Radar, DATATRAK Unified Experience and ERT Insights Cloud operate as a component of the trial's Electronic Data Capture (EDC) system (Table 6). Six SaaS RBM tools can operate independently or as an integrated function of the trial's EDC system (Table 6: items 14, 15, 18, 19 & 21). Six SaaS RBM tools operate independently to the trial's EDC system (Table 6: items 9, 16, 17, 20, 22–24).

3.4.2.3 Language of administration

All 24 RBM tools included in this review operate in the English language. Seven SaaS RBM tools are available in multiple languages (Table 6: items 9–15). The Risk

Assessment Tool (RAT) was developed by German academic clinical researchers and is available in both English and German formats(171). The Risk-Assessment Form (RAS) and accompanying tool is available in English and French formats(129).

3.4.2.4 Cost

The six-paper based RBM tools developed by academic and regulatory clinical researchers are available free of charge and can be downloaded from each organisation's webpage (Table 6: items 1, and 4–7). The Microsoft Excel version 2 of the Risk Assessment Categorization Tool (RACT) is also available free of charge and can be downloaded from the TransCelerate website(26). The risk assessment questionnaire used as part of the Early Bird RBM tool is provided free of charge on the Cyntegrity website(172). The 16 RBM tools included in this review that operate as SaaS must be purchased (Table 6: items 9–24). The costs of these SaaS are based on licence and hosting fees and trial specification, such as the number of study sites in the trial, the phase of the trial and the number of study participants.

3.4.2.5 Quality check process

The Risk Assessment Form (RAS) is the only tool to provide data demonstrating how its RBM strategy was tested for non-inferiority against 100% on-site SDV monitoring (see Table 6). The RBM approach in the RAS was less effective than 100% on-site SDV monitoring at detecting errors in the participant consent process, late notification of serious adverse events (SAEs) and incorrect application of participant's eligibility criteria and inaccurate reporting of the main study outcome (143). Similarly the ADAMON project is comparing the effectiveness of the RBM strategy directed by its risk assessment form against traditional intensive monitoring with frequent visits and 100% source data verification(171). ADAMOM is a cluster randomised study involving twelve different clinical trials that are randomised to either RBM or a traditional monitoring approach. The results of this study are expected in late 2016 (171). Currently Cyntegrity, the developers and providers of the Early Bird RBM tool are also conducting the PUEKS project – Process Optimisation in Clinical Trial Monitoring which aims to develop and validate a Risk- based Monitoring process using robust data-driven indicators(134).

Table 6: Characteristics of RBM tools

Author	Affiliated clinical trial organisation	Risk assessment tool	Publication/ Marketing Year	Country of Origin	Applicable clinical trial phase	Applicable to medical devices	Mode of administration	Language	Cost	Quality check process
1. Brosteanu et al [171]	Academic	Risk analysis form	2009	Germany	All	Yes	Paper based	English & German	None	**Ongoing:** Non-inferiority testing with traditional on-site SDV monitoring
2. Journot et al[129]	Academic & Regulatory	Risk-assessment scale (RAS)	2011	France	All	Yes	Paper based	English & French	None	RBM strategy tested for non-inferiority against traditional monitoring
3. MRC/DH/MRHA[28]	Academic & Regulatory	Risk classification method	2011	UK	All	No	Paper based	English	None	No
4. Nordic Monitoring Network (NORM) [27]	Academic	Risk Assessment Tool (RAT)	2015	Norway Denmark Sweden Finland	All	No	Paper based	English	None	No
5. Smith et al [169]	Academic	TORPEDO-CF: Risk analysis form	2014	UK	All	No	Paper based	English	None	No
6. Swiss Clinical Trial Organisation (SCTO) [170]	Academic	Risk assessment for risk-adapted monitoring	2015	Switzerland	All	Yes	Electronically via Microsoft Excel	English	None	No
7. Yee et al[173]	Academic	Masonic Cancer Centre (MCC) Risk	2012	USA	All	Yes	Paper based	English	None	No

		Assessment Checklist								
8. TransCelerate BioPharama Inc[26]	Biopharmaceutical - nonprofit organisation	Risk Assessment Categorization Tool (RACT)	2014	USA	All	Yes	Electronically via Microsoft Excel	English	None	No
9. Bioclinica(174)	Independent Software Vendor **(ISV)**	Bioclinica Compass RBM	2014	USA	All	Yes	Software as a service **(SaaS):** operates independent to EDC system	English-primary language but language can be changed to match trial specifications	Cost based on licence &hosting fees, trial duration & study sites, consultation services	In-house validation
10. DATATRAK International Inc[175]	**ISV**	DATATRAK Unified Experience	2000	USA	All	Yes	**SaaS-** it is a component of the EDC	Multiple languages including English, Kanji & Chinese	Hosting fees	In-house validation
11. ICON [176]	Contract Research Organization (**CRO**)	ICONIK	2011	Ireland	All	Yes	**SaaS**	Multiple languages including English	Hosting fees	In-house validation
12. JMP[177]	**ISV**	JMP® Clinical	2010	USA	All	Yes	**SaaS**	English & Chinese	Hosting fees	In-house validation
13. Medidata[178]	**ISV**	Targeted Source Data Verification (TSDV)	2014	USA	All	Yes	**SaaS**	All languages	Hosting fees	In-house validation
14. xClinical [179]	**ISV**	Marvin	2002	Germany	All	Yes	**SaaS:** can operate independently or can integrate with trial's Electronic Data Capture (EDC) system	Multiple languages	Cost based on no. of data items	In-house validation

15. Flex Databases[180]	**ISV**	Clinical Trial Management System	2005	Russia	All	Yes	**SaaS:** can operate independently or can integrate with EDC	English & multiple languages	Hosting fees, helpdesk, data storage & backup & training	In-house validation
16. Triumph Research Intelligence (TRI)[181]	**ISV**	OPRA	2013	USA	All	Yes	**SaaS:** typically operates as an independently to the EDC but uses EDC as a source of data to analyze	English	Hosting fees on a monthly basis	Fully validated
17. Cyntegrity[172]	**ISV**	Early Bird	2014	Germany	All	Yes	**SaaS: operates independent to system**	English	Cost depends on study size &phase. But free version of risk assessment questionnaire -RACT available on Cyntegrity website	In -house validation and as part of a scientific collaboration project- 'Process Innovation in Clinical Monitoring (PUEKS)
18. CluePoints[182]	**ISV**	Central Monitoring Platform	2014	Belgium & USA	All	Yes	**SaaS:** operates independent or can integrate with EDC system	English	Cost depends on no. of sites & participants, hosting	Technical & in-house validation via customer and in-house validation

									& consultation fees	
19. Remarque Systems[183]	**ISV**	Remarque	2016	USA	All	Yes	**SaaS:** can operate independently or integrated with EDC systems	English	Cost based on the number of participants, sites, duration and type of trial (e.g. phase of trial)	In-house validation
20. Algorics[184]	**ISV**	Acuity	2016	USA	All	Yes	**SaaS:** operates independent to EDC	English	Cost depends on no. of sites & participants, hosting & consultation fees	In-house validation
21. Kestrel Biologic[185]	**ISV**	iQROS	2011	Canada & USA	All	Yes	**SaaS:** can operate independently or integrated with EDC	Mainly English	Based on the trial's level of complication, enrolment and frequency of monitoring	In-house validation and system quality checks in trials
22. Clindata[186]	**ISV**	Clindate Cloud	2014	USA	All	Yes	**SaaS:** operates independent to ECD system	English	Based on system customization for a	In-house validation

									given study and subsequent monitoring fee	
23. Clinerion[187]	**ISV**	Quality Risk Radar	2011	Switzerland	All	Yes	**SaaS:** integrated with EDC system	English	Hosting fee determined by number of studies	In-house: computer software validation and vendor validation
24. ERT[188]	**ISV**	ERT Insights Cloud	2014	USA	All	Yes	**SaaS:** integrated with EDC system	English	Based on number of studies, users and the number of source systems to be connected	In-house and customer validation

3.4.3 RBM strategy informed by RBM tools

3.4.3.1 Baseline risk assessment process

Table 7 describes the process used by each of the 24 RBM tools to assess baseline risks in a clinical trial. All 24 RBM tools identified risks in the clinical trial protocol using a checklist of pre-determined risk categories. The six-paper based, and the two Excel powered RBM tools used a pre-determined risk assessment questionnaire to identify risks in a clinical trial (Table 7: items 1–8). Sixteen RBM tools, that operate as SaaS, applied a more flexible approach to risk assessment which allows for the identification of ad-hoc trial specific risks that are not pre-defined in the risk assessment questionnaire (Table 7: items 9–24). All RBM tools examined several similar risk categories that would negatively affect patient safety and the credibility of trial data. These categories included the safety profile of the IMP, the phase of the clinical trial under investigation, clinical trial medical procedures, pharmacovigilance reporting, profile of the study population and data collection procedures. Seven RBM tools based their risk assessment process on TransCelerate's RACT tool (Table 7: items 8, 12,13, 17, 19–21).

The risk indicators used by the 24 RBM tools were mapped onto an established risk indicator taxonomy for supervision of clinical trials of medicinal products (see Table 8). The taxonomy includes risk indicators that relate to 'What IMP' is under investigation, 'Who is conducting the clinical trial' and 'How' the trial is being conducted(133). Only 12 of the 24 RBM tools included in this review examined all 12 risk indicators listed in the taxonomy (Table 8 : items 4:, 5, 8, 9, 12, 13, 15, 17 –19, 21& 22).

3.4.3.2 Classification of clinical trial risk

The RBM tools included in this review used two methods to grade the risks identified during the risk assessment process (see Table 7). One method involved the assignment of an overall risk category to the clinical trial based on the types of risks identified during the risk assessment phase (Table 7: items 1–3, 5–7, 9 & 23). The risk categories most commonly used by the RBM tools were low, medium or high risk.

The Risk analysis form developed by Brosteanu et al. in 2009, used this method(171). This RBM tool recommends that a high risk score should be assigned to a trial that is either a Phase I trial or is using an IMP for an unlicensed indication (Table 7: item 1)(171). The subsequent risk mitigation strategy should focuse on controlling the overall risk of the clinical trial.

Nine RBM tools used a different method to classify risks which involved ranking each risk category individually (Table 7: items 4, 8,10,12,13,15,16,17 & 18). These RBM tools assigned an independent risk classification (e.g. low, medium or high) to each risk category identified during the risk assessment process. TransCelerate's RACT used this method and ranked each independent risk category based on its probability of occurring, how detectable the risk is and its impact (26). The overall risk score for each of the 13(+1) risk categories is calculated and the value determines whether the risk category is low, medium or high (Table 7: item 8)(26). The subsequent risk mitigation strategies focus on controlling individual risk categories.

Three SaaS operated RBM tools were able to rank risks using two systems. The first graded risks based on individual risk indicators and the second system applied an overall risk category to the clinical trial level (Table 7: items 19, 21 & 22). xClinical's RBM tool, does not assign risk classification because the company believes it is inappropriate for the software to assign a risk category and, instead, this needs to be completed manually by the study team (Table 7: item 14)(179).

3.4.3.3 On-site monitoring guideline

ICONIK was the only RBM tool that did not support on-site monitoring to mitigate clinical trial risk (Table 7: item 11)(176). Instead, another ICON software called the Error Capture and Action Tool (ECAT) can be used in partnership with ICONIK to guide on-site monitoring(189). The 23 other RBM tools recommend on-site monitoring strategies to mitigate risks identified during the risk assessment (see Table 7). The Risk Assessment Tool (RAT)(27) and the Risk Assessment Categorization Tool (RACT)(26) advised what types of risk categories should be controlled using on-site monitoring(Table 7: items 4 & 8). These risks include patient safety risks, data accuracy risks, staff training and internal site risks.

Six RBM tools provided explicit guidance for on-site monitoring based on a trial's risk classification and the stage of the trial (Table 7: items 1–3 & 5–7). For example, the Risk classification tool advised scheduled on-site visits were not required for low risk trials (Table 7: item 3).

Risks identified during on-site monitoring could be manually entered into seven of the SaaS based RBM tools (Table 7: items 10, 17–22). Cyntegrity's RBM tool, Early Bird, allows the clinical trial team to create an issue management system (IMS) ticket and assign it to the site and risk (Table 7: item 17)(172).

3.4.3.4 Centralised monitoring guideline

The MCC Risk Assessment Checklist was the only RBM tool included in this review that did not provide guidance for risks mitigation through centralised monitoring (Table 6: item 7)(173). Seven tools, five paper based and two Excel RBM provided information on how and what risks should be controlled through centralised monitoring activity (Table 7: items 1–6 & 8). These risks include patient safety risks, data ac- curacy risks, staff training and internal site risks (see Table 7). For example, the RBM tool developed by the Swiss Clinical Trial Organisation (SCTO), advised that protocol compliance could be monitored centrally for low-risk trials (Table 7: item 6)(170). These seven RBM tools did not provide guidance on suitable Electronic Data Capture (EDC) or clinical trial management system (CTMS) that a clinical trial should use to sup- port centralised monitoring(190). In contrast, the main function of the 16 SaaS RBM tools is to perform centralised monitoring (Table 7: items 9– 24).

3.4.3.5 Recommended process for systematic review of trial's risk profile

The paper based Risk Assessment Scale (RAS) was the only RBM tool included in this review that did not recommend a process for systematic review of the trial's risk profile (Table 7: item 2)(129). The other seven non-SaaS RBM tools provided varying level and types of advice for how a clinical trial team should manually reassess the trial's risk profile as the trial progresses (Table 7: items 1, 2–8). For example, TransCelerates's RACT suggests that the risk profile of a trial should be reassessed whenever the protocol is amended (Table 7: item 8)(26).

The SaaS based RBM tools included in this review provided functions that allowed for their software to reassess the risk in a trial automatically by systematically analysing electronic trial data (Table 7: items 9–19 & 21–24). For example, the Clinical Trial Management System from Flex Databases, performs real time risk analysis on both sub-sample and total sample analysis in accordance with predefined milestones/time- lines(180). If a risk indicator is notified, the trial team is alerted via email and system alert (Table 7: item 15).

Table 7: RBM strategy informed by RBM tools: risk assessment, risk classification and risk mitigation strategy (on-site & centralised monitoring).

Author	Categories of baseline risks assessed before the trial begins	Risk Classification of a clinical trial (CT)	Recommended On- site monitoring activity	Recommended Centralised monitoring activity	Recommended process for systematic review of a trial's risk profile
1. Brosteanu et al (171)	1. Potential risk associated with therapeutic intervention 2. Trial specific risk analysis - Patient related indicators 3. Trial specific analysis - Indicators of robustness Trial specific analysis - Site related indicators	The CT is assigned an overall risk category based on the results of the risk assessment as follows: **K3 – low/comparable risk**: Phase IV or IIIb trial, IMP relates to its licenced range of indicators. Trial has patient related critical indicator that can be controlled by on-site monitoring & at least one indicator of robustness **K2- intermediate risk**: Phase II or IIIb trial, IMP used for a new unlicensed indication. Trial has no patient related critical indicator that can be controlled by on-site monitoring & at least one indicator of robustness **K1- high risk:** Phase I trial. IMP is used for unlicensed indication. Trial has no patient related critical indicator that can be controlled by on-site monitoring	Schedule of on-site visits for: **K3 – low/comparable risk**: one annual on-site visit. Triggered on-site visits recommended if concerns emerge through centralised monitoring **K2- intermediate risk**: pre-study visit; initiation visits; first visit after 1-2 patients recruited; at least 3 routine on-site visits annually. Close out visits only if required. **K1- high risk:** pre-study visits; initiation visits; first visit after 1st patient enrolment; at least 6 routine on-site visits annually and close out visit.	Categories of risks to be monitored centrally: **K3 – low/comparable risk:** trial-specific documentation such as high level of inconsistencies or implausible data **K2- intermediate risk**: close central monitoring – no further guideline. **K1- high risk:** close central monitoring – no further guideline.	For-cause monitoring is recommended to deal with risks that emerge throughout the trials when irregularities that exceed a pre-defined tolerance limit are detected e.g. Serious Adverse Events (SAEs) are regularly reported late or incomplete
2. Journot et al(129)	1. Stage 1 – identifying the focus of the study and its characteristics i.e. IMP, study phase &	The CT is assigned an overall risk category based on the results of the risk analysis as follows:	Schedule of on-site visits for **Risk level A:** initiation visit if site is not known; routine on-site visits to check SAE	Categories of risks to be monitored centrally: **Risk level A:** verification of resources adequacy at	Not specified

	physiopathology techniques 2. Stage 2- Identifying one or more parameter increasing risk i.e. vulnerable study population	**A -Low risk:** Trial of low risk certified medical device**;** or an IMP outside it's licensed indications along with simple study questionnaires and minimally invasive medical intervention **B-normal risk:** Trial of low/moderate risk certified or uncertified medical device; or an IMP outside it's licensed indications along with technique or biopsy performed on an internal organ & use of questionnaire for severe medical condition **C-high risk:** Trial of moderate/high certified medical device**;** or an IMP outside its licensed indications involving the generalisation of a new surgical technique **D- very high risk:** Trial of moderate/high risk certified or uncertified medical device; or an IMP outside its licensed indications involving the development of a new surgical technique	management- number of routine visits not specified **Risk level B:** initiation visit if site is not known; 1st routine on-site visits when 10% of patients are recruited; additional triggered visits if issues identified **Risk level C:** initiation visit if site is not known; at least 1 annual visit to study sites and another visit when pre-determined recruitment levels are achieved; additional triggered visits if issues identified and site close-out visit **Risk level D:** not specified	investigator site; study initiation; verification of CRF, consent process, detection of unreported SAEs; administrative closure of study site **Risk level B:** verification of resources adequacy at investigator site; study initiation; administrative closure of study site; detection of unreported SAEs **Risk level C:** verification of resources adequacy at investigator site; study initiation; detection of unreported SAEs and CRF verification **Risk level D:** not specified	
3.MRC/DH/MRHA[28]	1. Risks to participant's safety in relation to the IMP 2. Phase of trial 3. IMP safety profile	The CT is assigned an overall risk category primarily based on the risk associated with the IMP: **Type A**: No higher than the risk of standard medical care	Schedule of on-site visits for: **Type A:** no requirement for scheduled on-site visits. Triggered on-site visits recommended if concerns emerge through centralised monitoring	Categories of risks to be monitored centrally: **Type A:** protocol adherence & data quality **Type B:** safety data quality & timeliness; protocol	Risk assessment and associated monitoring plans should be kept under review during the trial and modified as necessary if unanticipated risks emerge

	4. Risks to participants from clinical procedure specified by the protocol 5. Data protection risks 6. Risks to the reliability of study results	**Type B**: Somewhat higher than the risk of standard medical care **Type C**: Markedly higher than the risk of standard medical care	**Type B:** triggered visits for poor data return or protocol adherence concerns & unusual level of Serious Adverse Events (SAE) **Type C:** intense scheduled on-site monitoring (amount not specified)	adherence and trial data quality **Type C:** safety data quality & timeliness; protocol adherence and trial data quality	
4.Nordic Monitoring Network (NORM) (27)	1. Study Organisation and governance 2. Training (staff) 3. Trial subjects' rights and safety 4. Data (protection/validation) 5. Protocol procedures 6. Study Drug/IMP 7. Safety Reporting (Pharmacovigilance) 8. Impact (study results) 9. Other	Each risk category is independently ranked based on the severity (1-3 scale) and probability (1-3 scale) of the risks within each category. For example, when assessing risk **Category 6- Study Drug/IMP**: the risks associated with handling the study drug are classified on the probability of negative outcome emerging and their severity	Categories of risks to be mitigated by on-site monitoring: • Study Organisation and governance • Training (Staff) • Trial subject's rights and general safety • Protocol Procedure • Study drug/IMP • Impact of study results	Categories of risks to be monitored centrally: • Data – data protection • Protocol Procedure through the electronic clinical report form (eCRF) • Safety Management	To be considered based on the findings of each routine on-site visit
5.Smith et al [(169)]	1. Patients Hazards/Research Staff Hazards (right and safety) 2. Study Hazards (Completion and Reliability) 3. Organisational Hazards	The CT is assigned an overall risk category based on the results of the risk analysis as follows: **Low risk**: CT has a risk score of ≤ 33% **Moderate risk**: CT has a risk score of ≥ 34 to ≤ 67% **High risk**: CT has a risk score of ≥68 to ≤ 100%	Example given for **low risk** TORPEDO-CF trial. Schedule of on-site visits for: • Green light visit • Triggered visits • Study close-out visit	Example given for **low risk** TORPEDO-CF trial. Ongoing schedule of central monitoring: • Consent forms • Patient recruitment • Protocol deviations • Missing primary outcome data • Adverse Events (AE) • Case report forms • Data entry process	Frequency and review of trial monitoring should be amended during the trial if issues that require immediate action are identified

6.Swiss Clinical Trial Organisation (SCTO) [170]	1. Potential risk of therapeutic intervention in comparison to standard of medical care 2. Potential trial participant-related critical indicator 3. Robustness related indicators – "hard primary endpoints" and/or simple clinical trial procedure	The CT is assigned an overall risk category based on the results of the risk analysis as follows: • **Low risk:** IMP is authorised in Switzerland & trial has at least one indicator of robustness • **Intermediate risk:** IMP is authorised in Switzerland & trial has no indicator of robustness • **High risk:** IMP not authorised in Switzerland and trial has no indicator of robustness	Schedule of on-site visits for: • **Low risk trial:** pre-trial visit; annual monitoring visit to review Trial Master File(TMF) and Sites Files (SF) and close out visit • **Intermediate risk trial:** pre-trial visit; 1-3 monitoring site visits annually to review TMF & SF and close out visit • **High risk trial:** pre-trial visit; site-initiation visits; 2-8 monitoring site visits annually to review TMF & SF and close out visit	Categories of risks to be monitored centrally: • **Low risk trial:** site initiation and consistency checks (protocol compliance; Case Report Forms (CRFs) and clinical research participant information) • **Intermediate risk trial: site initiation and consistency checks** • **High risk trial:** Consistency checks	An additional risk assessment is required if the trial undergoes substantial amendments
7.Yee et al[173]	1. Phase of trial (phase I or II, or pilot study) 2. Known toxicity of IMP 3. Unknown toxicity of IMP 4. Origin of trial agents, devices or processes 5. Does trial involve an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE) 6. Complexity of processes involved in the trial i.e. IMP administration 7. Experience of Principle Investigator	The CT is assigned an overall risk category based on the results of the risk analysis as follows: • **Low risk:** no risks identified during risk assessment • **Moderate risk:** one of the following risks are present - Pilot or phase II trial - PI has <2 completed trials - the trial procures are complex • **High risk:** one of the following risks are present - Phase I trial - Unknown IMP toxicity - High known IMP toxicity	Schedule of on-site visits for: • **Low risk trial**: annually review from Data Safety Monitoring Committee (DSMC) • **Moderate risk trial:** Twice yearly monitoring by both trial monitor and DSMC • **High risk trial:** Twice yearly monitoring by trial monitoring and queerly DSMC visits	Not discussed	For high enrolling studies (recruitment goal >100 subjects)-100% SDV is advised for first 50 subjects recruited. If no issues emerge the Data Safety Monitoring Committee (DSMC) may subsequently allow SDV monitoring activity to only be performed on 10% of subject data during the remaining recruitment period

		- New Drug Application (IND) or an Investigational Device Exemption (IDE)			
8.TransCelerate BioPharama Inc[26]	1. Safety related to IMP 2. Study phase 3. Complexity of study i.e. no. of study sites 4. Study population 5. Technology 6. Data collection/CRF source 7. Endpoints 8. Organisational experience 9. Investigational product/study medication 10. IMP logistics/supply chain 11. Blinding 12. Operational complexity 13. Geography of study sites Other risks	Each risk category is independently ranked based on its probability of occurring (1-3), how detectable the risk is (1-3) and its impact (1-.3) The overall risk score for each the 13(+1) risk categories is calculated and depending on the value, the risk categories are classified as: • Low risk • Medium risk • High risk	Categories of risks to be mitigated by on-site monitoring: • Safety risks • Study phase • Complexity • Subject population • Data collection- CRF source • Endpoints • Organisational experience • IMP logistic/supply chain • Blinding • Operational complexity • Geography of study sites	Categories of risks to be monitored centrally: • Safety risks • Complexity • Technology • Subject population • Data collection- CRF source	The risk profile of the trial should be reassessed whenever the protocol is amended
9.Bioclinica(174)	The tool has 46 standard risk assessment (KRIs) questions which are quantitative and qualitative in nature Additionally, KRIs can be added to the system of required by the trial.	An overall site quality score is calculated by Compass based on the assignment and weighting of KRI's	Tool supports routine and triggered on-site monitoring-process is unique to each trial and is determined by the trials KRIs, study SOPS and study team's business plan It is not possible to manually enter issues captured during on-site into the Compass software	Tool supports centralised monitoring – process is unique to each trial and is determined by the trials KRIs, study SOPS and study team's business plan	Compass performs monthly risk assessments on centrally stored electronic trial data using inbuilt algorithm assessing the study sites performance against KRIs. Subsequent risk concerns are flagged, and appropriate action is requested via on-screen or email notification
10.DATATRAK International Inc[175]	Risk can be pre-determined in the study design by selecting forms that require or do not	Each risk category is independently ranked. The DATATRAK Unified Experience evaluates risk based on the information provided by the	No -but DATATRAK Unified Experience has a data management function which provide the ability to enter and track manual events that ate	Tool supports centralised Monitoring by evaluating incoming data attributes and to determine future risk profiles.	The software provides real-time analysis to evaluate risk and determine the appropriate risk-based approach. Risks include site

	require SDV, Data Review or eSignature. Risk can also be calculated based on a patent-pending User Score which evaluates the site user's quality of data entry to determine how much review is required. The system also supports dynamic percentage risk	trial data such as participant case form and the activity of the monitoring team to determine the risk factors for each individual trial that must be mitigated during monitoring.	identify during on-site monitoring		and clinical trial team activity. **However,** the system does not currently support proactive signalling based on changes in the risk profile.
11.ICON [(176)]	Risks are identified using various analytics and visualization for identifying trends & signals	Not disclosed - information protected under Confidentiality Data Agreement (CDA)	Tool does not support on-site monitoring – on-site monitoring is supported by complimentary ICON software called the Error Capture and Action Tool (ECAT)	Tool supports centralised monitoring	Not disclosed
12.JMP[(177)]	Risks are measured using **TransCelerate's** risk indicators[(26)] and organise by different Clinical Data Interchange Standards Consortium(CDISC)[(191)] domains and custom criteria	Each risk category is independently ranked. Risk is not assessed at the clinical trial level. Goal is to identify sites within a clinical trial that are underperforming	Tool supports routine and triggered on-site monitoring	Tool supports centralised monitoring	Not disclosed
13.Medidata[(178)]	Risks are measured using an edited version of **TransCelerate's** risk indicators as follows: • Study design complexity • Patient population • Investigational Medicinal Product (IMP)	Each risk category is ranked independently as either: • Low risk • Medium risk • High risk	Tool supports routine and triggered on-site monitoring	Tool supports centralised monitoring	Not disclosed

14.xClinical [179]	Risk is evaluated at each trial center by the data manager according to set risk then Marvin (RBM tool) applies a predefined SDV pattern	No – Marvin does not assign risk classification as company believe it is too risky for software to assign a risk category – this is instead completed manually by study team	Marvin applies a predefined SDV pattern for on-site monitoring	Tool supports centralised monitoring	Risks are reassessed via a manual report and risk concerns are notified by report/email
15.Flex Databases[180]	Flex Databases measure risk using a risk assessment questionnaire customized to track risk indicators in each trial	Each risk category is independently ranked. Trial sites are assigned an individual risk level which is determined by the number of risk factors in each trial site	Supports triggered on-site monitoring to mitigate risks	Tool supports centralised monitoring through real time analysis of trial data collected electronically	The system performs real time risk analysis on both sub-sample and total sample analysis in accordance with predefined milestones/timelines. If a risk indicator is notified the trial team is alerted via email and system alert
16.Triumph Research Intelligence (TRI)[181]	The OPRA system measures risks using statistical algorithms and adaptable KRIs	Each risk category is independently ranked. Risk category assigned to each KRI and each study site	Yes- software will guide activities that should be performed during on-site monitoring	Tool supports centralised monitoring, software will guide activities that should be performed through centralised monitoring	The OPRA system reassess the trial's risk profile each time data is entered into the system
17.Cyntegrity[172]	EarlyBird 's risk assessment based on **TransCelerate's** RACT and Metric Champion Consortium (MCC) and retrospective assessment of already finished trials.	Each risk category is independently ranked. Risk classification based **TransCelerate's** RACT and Metric Champion Consortium (MCC)	Yes – the clinical trial team can create an issue management system (IMS) ticket and assign it to the site and risk	Tool supports centralised monitoring. Real time analysis for operational & site level risks. Risk profiles are adjusted every night. Study level risks are assessed quarterly or every 6 months.	Risk concerns are flagged via a built-in (IMS) with escalation logic, issue priorization, internal communication, root cause analysis and mitigation plan.
18.CluePoints[182]	The Central Monitoring Platform assesses baseline risk using pre-determined KRIs, risk algorithm, risk assessment questionnaire	Each risk category is independently ranked. Risk category is assigned to each individual risk and an overall risk score is assigned to a trial	Yes- it informs on-site monitoring by identifying those sites most at risk and why those sites need priority monitoring attention. Issues that are identifying during on-site monitoring can be	Tool supports centralised monitoring. Key risk indicators are assessed using real time analysis or every 1-2 weeks depending on the client's preference. Overall data quality assessment is	Risk concerns are flagged via an in-built Action Tracking Management System

			manually entered into the software	performed monthly or every 2-4 months	
19.Remarque Systems[183]	Remarque RBM assesses baseline risk using **TransCelerate's** RACT	Risk categories can be assigned to either individual risk indicator or overall risk by categories, by patient or site,	Yes- if a risk concern is flagged, Remarque RBM can create an action item that requires onsite monitoring	Tool supports centralised monitoring, identified risks are continuously monitored using central data	The system supports continuous risk assessment and If a risk concern is flagged Remarque alerts the user through machine learning algorithms and through programmed triggers
20.Algorics[184]	Risks are measured using **TransCelerate's** RACT, but Acuity can include additional risks as per client's request	Not disclosed	Yes- system can capture data collected during on-site monitoring	Acuity uses subject and site-specific dashboards and alerts to monitor critical data points in real time for scheduled and ad-hoc reviews	The system uses algorithms to reassess site risk profiles and predictive trending drive focused site monitoring and provide traceability from assessment to action
21.Kestrel Biologic[185]	iQROS assesses risk using Failure Mode Effect Analysis (FMEA) and can incorporate **TransCelerate's** RACT tool	Risk categories are assigned to individual risk indicators and can be aggregated to the trial level	Yes – system creates a to list of monitoring activates that can be completing via on-site monitoring. Data that is collected via on-site monitoring can be manually entered into the system	Tool supports centralised monitoring – software stored all data collected from monitoring activity	The system does not reassess the risk level, instead the status of each individual risk mitigation is shown, and the risk level cab be updated at any time. Subsequently iQROS will create a to-list if monitoring activities the clinical trial team must action
22.Clindata[186]	Clinidata Cloud assesses risk using a risk assessment questionnaire, KRIs,machine learning risk predictive algorithm	Risk categories are assigned to individual risk indicators or to trial level	Yes- onsite monitors can use specifically designed risk monitoring screens to enter their observations and the system then triggers remediation actions if risk concerns are flagged	Tool supports centralised monitoring; the system runs 100% real time reassessment of entire clinical trial data using Machine learning and mining algorithm	If risk concerns are flagged, the system sends real time mobile alerts such as emails to the trial team and this activity in documented in pre-defined scheduled reports

23.Clinerion[187]	Quality Risk Radar (IQR) covers a holistic risk assessment starting with the study protocol at concept stage, followed by regular trial site assessments which enable targeted monitoring	Overall risk classification. QRA calculates risk per patient safety as well as the data integrity per trial site and per study protocol. Additional risk levels per trial sites are: structural risk, procedural risk and risk details (KRI level)	System can signal risk concerns that require mitigation through onsite monitoring. Presently, manual addition of risk information cannot be entered into the system	Tool supports centralised monitoring – system monitors central data at regular intervals to reassess the risk profile of the trial	Risk signals are refreshed after arch re-assessment of risk and displayed in real time throughout the system dashboards. In addition, email notifications can be configured as required
24.ERT[188]	ERT Insights Cloud allows Customers to configure/ weight pre-determined KRIs. Protocol assessments performed by the customer, and study-specific algorithms and analytics are developed using protocol or endpoint-related risk criteria.	Risk categories are limited to the KRI (key risk indicator)	Yes, the tool includes electronic monitoring visit report, scheduling, and alerts. CRAs can be notified of the need for a monitoring visit. The system can track that the visit has taken place, as well as integrate information from the monitoring report back into the system.	Yes, the tool provides real time analysis of risk through centralised monitoring	Risk indicators can be weighted with temporal parameters for each site depending on investigator experience or other contextual information. Composite scores are generated by weighting sites against each other.

Table 8: RBM tools mapped to the Risk indicator taxonomy for supervision of clinical trials on medicinal products

Author	**A. What: IMP** A1. Knowledge and IMPs in human A2. Treatment aspects A3. Potential large patient population A4. High- risk IMP	**B. By whom: investigator, clinical trial site, and sponsor** B1. Professionalism B2. Reputation B3. Level of experience	**C. How: trial design** C1. Participant characteristics C2. High burden for participants related to study procedures C3. Duration of treatment (>1month) C4. Design (protocol) C5. Conduct
1. Brosteanu et al [171]	All (A1-A4)	None	All (C1-C5)
2. Journot et al[129]	All (A1-A4)	None	All (C1-C5)
3. MRC/DH/MRHA[28]	All (A1-A4)	None	All (C1-C5)
4. .Nordic Monitoring Network (NORM) (27)	All (A1-A4)	All (B1-B3)	All (C1-C5)
5. Smith et al [169]	All (A1-A4)	All (B1-B3)	All (C1-C5)
6. Swiss Clinical Trial Organisation (SCTO) [170]	All (A1-A4)	Only B3	All (C1-C5)
7. Yee et al[173]	All (A1- A4)	Only B3	All (C1-C5)
8. TransCelerate BioPharama Inc[26]	All (A1-A4)	All (B1-B3)	All (C1-C5)
9. Bioclinica(174)	All (A1-A4)	All (B1-B3)	All (C1-C5)
10. DATATRAK International Inc[175]	Some (A1 & A2)	Some (B1 &B2)	Some (C1-C4)
11. ICON [176]	Not disclosed	Not disclosed	Not disclosed
12. JMP[177]	All (A1-A4)	All (B1-B3)	All (C1-C5)
13. Medidata[178]	All (A1-A4)	All (B1-B3)	All (C1-C5)
14. .xClinical [179]	None	None	None
15. Flex Databases[180]	All (A1-A4)	All (B1-B3)	All (C1-C5)
16. Triumph Research Intelligence (TRI)[181]	Some (A1-A3)	Some (B1 &B2)	Some (C1, C3-C5)

17. Cyntegrity[172]	All (A1-A4)	All (B1-B3)	All (C1-C5)
18. CluePoints[182]	All (A1-A4)	All (B1-B3)	All (C1-C5)
19. Remarque Systems[183]	All (A1-A4)	All (B1-B3)	All (C1-C5)
20. Algorics[184]	Some (A2-A3)	Some (B3)	All (C1-C5)
21. Kestrel Biologic[185]	All (A1-A4)	All (B1-B3)	All (C1-C5)
22. Clindata[186]	All (A1-A4)	All (B1-B3)	All (C1-C5)
23. Clinerion[187]	Some (A2- A4)	Some (B1 & B3)	Some (C2 – C5)
24. ERT[188]	None	None	Some (C3 & C4)

3.5 Discussion

3.5.1 Main findings

This systematic review identified 24 RBM tools that fulfilled the OECD classification. Accordingly, these tools can identify and assess clinical trial risks and recommend appropriate procedures and strategies to mitigate the risks identified(10). Our review did not find a standardized approach for examining the baseline risks in a clinical trial protocol. The risk assessment process developed by TransCelerate BioPharma Inc. appears to be the most operational as it has been replicated by six other RBM tools (see Table 7). We only identified 12 of RBM tools that assessed the 12 fundamental risk indicators listed in a recently published risk indicator taxonomy for supervision of clinical trials on medicinal products (see Table 8)(133). This finding strongly suggests that a gold standard approach to risk assessment has not yet been determined. However, despite the difference in the composition of the risk categories, most of the RBM tools evaluated risks associated with the safety profile of the IMP, the phase of the clinical trial and the data collection process. These risks correspond with ICH-GCP's monitoring demands to ensure the rights and well-being of human subjects are protected and the reported trial data are accurate, complete and verifiable from the source document(11).

The majority of RBM tools included in our review provided comprehensive guideline or functions for risk mitigation through on-site and centralised monitoring. This is important because the new ICH-GCP guideline states that RBM should be a mix of

centralised and on-site monitoring practices implemented specifically to control the risk identified during the risk assessment(12, 128).

Unlike on-site monitoring, which was introduced with ICH-CGP in 1996, centralised monitoring is still relatively new to clinical trials(130). This process involves checking electronic clinical trial data for errors and is performed primarily on a trial's Electronic Data Capture (EDC) systems(192). The paper-based tools included in this review did provide guidance for centralised monitoring, but they did not give examples of EDC systems to support their recommendations (see Table 6). In comparison, the 16 RBM tools that operate as Service as a System (SaaS) could function either independently or as an integrated component of a trial's EDC system (see Table 6). However, it should be noted that some of the SaaS RBM tools did not allow for manual events to be entered into their systems. Consequently, if an on-site monitor identifies risks, for example, relating to how study medication is stored, this information cannot be added to the SaaS system and so a link between on-site and centralised monitoring activity cannot be formed.

The ICH-GCP addendum states that RBM is a continuous process(157). Therefore, it is not sufficient for a RBM tool to simply assess baseline clinical trial risks. Instead a risk assessment should be carried out systematically throughout the life cycle of the study which involves a concurrent review of trial data collected from on-site and centralised monitoring(157, 192). Several of the SaaS RBM tools offered real time analysis for operational and site level risks. Concerns are then flagged by the system via a built-in Issue Management System (IMS) that issues internal communication alerts to the trial team(172). This computer aided function is not provided by the paper based RBM tools.

The 24 RBM tools included in this review can be divided into three categories based on their mode of administration: paper-based, powered by Microsoft Excel or operated as a Service as a System (see Table 6). It is not clear which mode of administration provides the most effective and efficient RBM strategy. They all had different merits in terms of cost, administration and function. The paper based Risk Assessment Scale (RAS) was the only tool to prospectively test it's RBM strategy for

non-inferiority compared to more traditional monitoring methods, such as 100% on-site SDV(143). However the RAS was shown to be less effective at detecting errors in the consent process, SAE reporting, application of participant's eligibility criteria and reporting of main study outcomes than traditional monitoring(143). Thus, a superior RBM tool or RBM approach was not identified in this review. Despite the availability of a range of paper based and computer aided RBM tools, the comparative effectiveness of these tools needs to be examined. This might be done through, for example, the embedding of methodology study in a large multi-centre clinical trial. This type of research would operate as a SWAT (Study Within A Trial) to provide a practical cost efficient approach to prospectively compare the validity of the two types of RBM tools(193, 194).

In the coming months and years, the new ICH-GCP addendum and EU Clinical Trial Regulation are poised to make RBM the preferred method for clinical trial monitoring(23, 128). The lack of a uniform approach may make it difficult for sponsors to decide which RBM tool they should use when developing a RBM plan. To help overcome this challenge, we applied the findings of our review to the ICH-GCP and OECD RBM guidelines and developed four criteria to considered when choosing a RBM tool(10, 23). These are:

1. Ensure the RBM tool's baseline risk assessment process examines the risk indicators set out in the Risk indicator taxonomy for supervision of clinical trials on medicinal products(133).
2. Ensure the RBM tool can support both on-site and centralised monitoring. For SaaS tools ensure that on-site monitoring data can be entered manually into the system(192).
3. Ensure the RBM tool provides a process for systematic review of the trial's risk profile(23).
4. Ensure the RBM tool is cost efficient i.e. the paper-based tools are available free of charge however they need the support of an EDC system to perform centralised monitoring.

3.5.2. Strengths and limitations

Our review is the first to systematically identify and compare academic and commercial RBM tools for clinical trial monitoring. It will make a major contribution

to the literature on RBM and provide RBM guidance to the global clinical trial community. Our findings will support the OECD's goal of ensuring appropriate and harmonised understanding of risk assessment(32).

Despite the comprehensiveness of this review it was not possible to capture all relevant material, such as unpublished in-house Standard Operating Procedures (SOPs) for RBM. Information on the commercially developed tools was in some cases limited as these organisations are protected under confidential data agreements. It must also be noted that our review was conducted before the ICH-GCP Addendum was published, and the release of the new ICH-GCP guideline in late 2017 may lead to an increase in the number of RBM tools. The European Clinical Research Infrastructure Network (ECRIN) webpage operates a RBM toolbox which contains a regularly updated list of primarily free paper- based RBM tools which may be useful to anyone wishing to stay updated on advancements in RBM tool development(195).

3.5.3 Conclusion

There is increasing recognition of the need to improve the quality and efficiency of clinical trials so that they can provide reliable and robust evidence needed by decision makers in health care who are faced by increasing demands and greater pressure on resources(150). This includes work to reduce waste in research, improve the selection of outcomes to measure and ensure that patients are more involved in all aspects of the trial(196-198). Alongside this, the resources put into the monitoring of a trial need to be proportionate to the risks associated with that trial(199). The Sensible Guideline Conference, held in Washington in 2007, first recommended that each new trial should conduct a risk assessment before developing a monitoring plan(156). Since 2007, risk assessment and, accordingly, RBM has gained acceptance among the global clinical trial community. In 2012, the UK registered Clinical Trial Units (Clinical trial units) stated that 53% of all their registered trials conducted a risk assessment to determine the level of monitoring(200). Similarly, a global survey conducted by the Metrics Champion Consortium (MCC) in 2013 identified a growing appetite for RBM among academic and commercial clinical trialists(25). However, despite its international recognition, best practice guidelines for RBM do not

exist(10). This review was conducted in anticipation of the forthcoming ICH-GCP Addendum that will elevate RBM to the forefront of clinical trial monitoring(23).

Chapter 4. Perceived barriers and facilitators to Risk Based Monitoring in academic-led clinical trials: a mixed methods study

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This paper was published in the journal *Trials* in 2017, please see Appendix H.

4.1 Abstract

Background: In November 2016, the ICH published a requirement for sponsors to develop a systematic, prioritised, risk-based approach to monitoring clinical trials. This approach is more commonly known as risk-based monitoring (RBM). However, recent evidence suggests that a 'gold standard', validated approach to RBM does not exist and it is unclear how sponsors will introduce RBM into their organisations. A first step needed to inform the implementation of RBM is to explore academic trialists' readiness and ability to perform RBM. The aim of this paper is to identify the attitudes, and perceived barriers and facilitators to the implementation of RBM in academic-led clinical trials in Ireland.

Methods: A mixed-methods, explanatory sequential design, with quantitative survey followed by semi-structured interviews. Academic clinical researchers (*N*=132) working in Ireland were surveyed to examine their use and perception of RBM. A purposive sample of survey participants (n=22) were then interviewed to gain a greater insight into the quantitative findings. The survey and interview data were merged to generate a list of perceived barriers and facilitators to RBM implementation, with suggestions for, and solutions to, these issues.

Results: Survey response rate was 49% (132/273). Thirteen percent (n=18) of responders were not familiar with the term risk-based monitoring and less than a quarter of respondents (21%, n=28) had performed RBM in a clinical trial. Barriers to RBM implementation included lack of RBM knowledge/training, increased costs caused by greater IT demands, increased workload for trial staff and lack of evidence to support RBM as an effective monitoring approach. Facilitators included participants' legal obligation to perform RBM under the new ICH-GCP guideline, availability of RBM guidance and perception of cost savings by performing RBM in future trials.

Conclusion: The results of this study demonstrate a need for training and regulatory-endorsed guideline to support the implementation of RBM in academic led clinical trials. The study provides valuable insights to inform interventions and strategies by policy makers, and clinical trial regulators to improve RBM uptake.

4.2 Introduction

In 1996, the International Conference on Harmonisation (ICH) published the first Good Clinical Practice guideline (GCP) for clinical trial conduct(11). Under ICH-GCP, sponsors in America, China and the European Union are legally obliged to monitor their trial activity(11). Monitoring aims to protect the rights and well-being of trial participants, support accurate data collection and ensure compliance with regulatory requirements(11). Traditionally, trials were monitored through intensive on-site monitoring visits with 100% source data verification (SDV)(105). SDV can be a laborious task because it involves the validation of data presented in Case Report Forms (CRFs) against original source data such as consent forms, irrespective of the trial's risk profile(105). Risks associated with the Investigational Medicinal Product (IMP), the vulnerability of the study population and the robustness of the study design are not considered when developing a traditional trial monitoring plan (105, 164).

In recent years the scale, complexity, and cost of clinical trials have increased beyond the scope of the original ICH-GCP(23). In November 2016, the ICH published the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) to respond to the changing clinical trial landscape(23). Under the revised ICH-GCP guideline, risk based monitoring (RBM) was recommended as an alternative to 100% SDV on-site monitoring(23). RBM incorporates both centralised monitoring conducted off-site through an examination of data captured on an electronic data capture system (EDC) and on-site monitoring practices that are proportional to the risks associated with the clinical trial(28). These risks relate to the Investigational Medicinal Product (IMP), the study population, research team expertise and the robustness of the study design(101, 129). When developing a RBM plan, the trial's protocol must be formally assessed to identify risks within the trial that can be mitigated through either on-site and/or centralised monitoring(170). Accordingly, risk assessment is the cornerstone of RBM(26). The emphasis on RBM is due to the assumption that it prevents waste of valuable clinical trial resources, such as study budget and staff time, on unnecessary monitoring activity that does not improve participant safety or data quality(30, 156).

The Organisation for Economic Co-operation and Development (OECD) recommends that clinical researchers use a RBM tool when developing a RBM plan(10). Such tools have two functions: first they support the assessment of risk in a clinical trial protocol and second they provide guidance for subsequent monitoring activity (on-site/centralised) that can mitigate the risk identified(10). We recently published a systematic review that identified 24 RBM tools that met the OECD's criteria(132). However there were many differences between the tools in terms of mode of administration (paper based versus software as a system), the baseline risk assessment process and guidance for on-site and centralised monitoring (132). For example, the Medicines and Healthcare Regulatory Agency (MHRA) advise 100% centralised monitoring for low risk phase III trials, while the Swiss Clinical Trial Organisation (SCTO) advise both on-site and centralised monitoring for similar low risk trials(28, 170).

In the absence of a 'gold standard' approach to RBM, it remains unclear how sponsors will implement it into their clinical trial units(201). Given this context, it is important to establish how prepared academic trialists are to perform RBM(170). Presently, Ireland does not have a national strategy to support the introduction of RBM into its publicly funded, academic run clinical trial units. A first step in the development of such a strategy involves the identification of academic trialists' readiness and ability to perform RBM(201). In this study we explore the experience of, attitudes to, and perceived barriers and facilitators associated with, the implementation of RBM in academic led clinical trial units in Ireland.

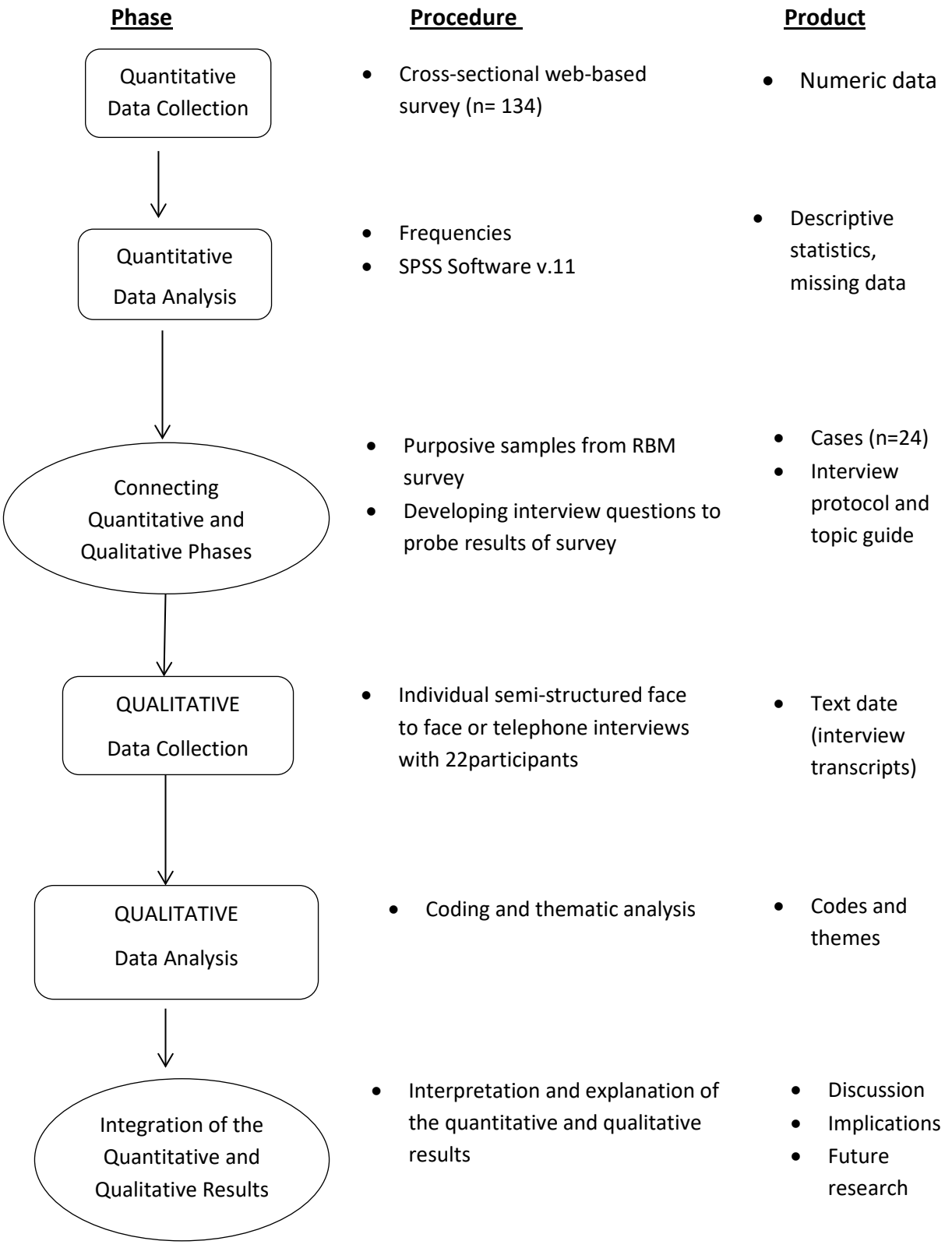
4.3 Methods

4.3.1 Design

We used a mixed methods explanatory sequential design. This design occurs in two distinct but interactive phases (202). It begins with the collection and analysis of quantitative data, followed by qualitative data collection and analysis to further explore the quantitative results (see Figure 7)(202). In this first study, methods were combined for complementarity, where each method addressed a different aspect of

the research question. The quantitative phase collected numerical data on the uptake of RBM in Ireland and its associated uses. The quantitative results facilitated sampling and development of the subsequent qualitative phase which further examined the barriers and facilitated associated with RBM.

Figure 6: Study design- mixed methods sequential explanatory design procedure(202)



4.3.2 Phase 1— Quantitative Surveys

Survey development: The study survey was adapted from the Clinical Trials Transformation Initiative (CTTI) monitoring questionnaire(203). The CTTI questionnaire contained 55 questions, collecting information on institutional demographics, overall study oversight methods, the use of risk- based monitoring, factors that influence risk assessment processes, and details of on-site and centralised monitoring practices(203).

Our survey is a shortened and modified version of the CTTI questionnaire. Questions pertaining to a trial's governance and verifications performed during on-site monitoring visits were excluded from our survey as they were not relevant to the current study. Our study also included additional questions on RBM tools which were not explored in the CTTI survey. In total our survey contained 20 questions. These include question regarding the participants' demographics and their experience and understanding of the three primary components of RBM which are 1) risk assessment 2) on-site monitoring and 3) centralised monitoring. A number of questions focused on respondent's clinical trial experience since the introduction of the European Communities-Clinical Trials on Medicinal Products for Human Use Regulations to Ireland in 2004(37). The full survey can be found in Appendix C.

The survey questions required responses that were either yes/no, multiple choice or open ended. Before distribution, the survey was pilot tested with a sample of 10 clinical researchers. The purpose of the pilot test was to make sure participants could understand and complete the survey. Further survey modification was not required after the pilot test.

Recruitment: The Health Research Board-Clinical Research Coordination Ireland (HRB-CRCI) is an independent, integrated, national clinical research network(64). It was established in 2014 to provide centralized support in the conduct of multicenter clinical trials across Ireland(64). Currently the HRB-CRCI operates as a collaborative partnership with five Clinical Research Facilities/Centers (CRF/C) based in five universities across Ireland(64). Researchers working in the CRF/Cs were eligible to participate in the survey. Participants included principle investigators (PI),

pharmacists, study doctors, nurses, project and quality managers, study monitors and biostatisticians.

Data Collection: The survey was administered via Survey Monkey, an online cloud-based survey development software(204). Participants received the survey invitation via an email sent from the Director of the Clinical Research Facility, Cork. This email was sent to participants between February and April 2016. It contained an online link to the survey. One reminder email was sent to all non-responders, three to six weeks after the initial email. The online survey was open for ten months from February to November 2016. However, 70% of survey responses were collected between February and June 2016.

Data analysis: Data captured in Survey Monkey were downloaded into Excel and then exported into SPSS version 11 for analysis.

4.3.3 Phase 2 — Qualitative Interviews

Methodology: Thematic analysis was used to identify barriers and facilitators to the implementation of RBM in participants' past, present and future clinical trials(205).

Recruitment: Recruitment took place over four weeks from 26th September to the 24th October 2016. Eligible participants were identified from respondents to the online survey, who had answered survey question 8.4, 9,3 or 10.2; 'Since 2004, have you implemented a risk-based monitoring plan in a clinical trial'. Responders of this question (n=107) were grouped into three categories (A, B or C) based on their response; **Group A** answered 'Yes'; **Group B** answered 'No'; and **Group C** answered, 'I am not familiar with the term 'Risk-based monitoring'.

Sampling: A purposive sample (n=24) of different clinical researchers (PIs, nurses, doctors, monitors, pharmacists, managers, biostatisticians) were selected from Groups A (n=8), Group B (n=8) and Group C (n=8) and invited to participate in the interviews via an email invitation. Two participants declined the invitation due to work commitments.

Setting: Face to face or telephone interviews (if participant was not available for a face to face interview) were conducted by an independent researcher (CH) from 7th October to the 29th November 2016. Face-to-face interviews were conducted in a private room in each participant's work place.

Data Collection: A semi-structured topic guide was developed to guide data collection. The topic guide was based on the results from Phase 1. The topic guide included open-ended questions including: the participant's most recent clinical trial experience including how this trial was monitored; their understanding and attitudes towards RBM; foreseen benefits and limitations of RBM; and factors that would facilitate or hinder them from implementing RBM in future trials. The topic guide was piloted on three clinical researchers based in the Clinical Research Facility, Cork and minor revisions were made. Revisions involved the inclusion of three questions pertaining to participants past clinical trial monitoring experience. These questions were included to gain a greater insight into the participant's clinical trial experience. The full topic guide can be viewed in Appendix C.

All participants received a Patient Information Leaflet and consent was obtained from all participants for their interview to be audio-taped and content to be used for research purposes. Interviews lasted between 20-35minutes. Data saturation was reached when additional information relating to barriers and facilitators to RBM implementation was no longer obtained from interview participants(206). Data saturation was assessed independently for Group A, B and C. Data saturation was reached for **Group A** after interview 4, **Group B** after interview 5 and **Group C** after interview 3. However, all scheduled interviews were conducted, transcribed and analyzed.

Data analysis: Interviews were audio recorded and transcribed verbatim. Transcribed interviews were coded and analyzed by two coders CH (epidemiologist and clinical trial methodologist) and ER (social policy researcher) using the qualitative data analysis software NVivo(207). The analysis followed the six phases of thematic analysis outlined by Braun and Clarke which include familiarization with the data,

generating initial codes, searching for, naming, defining and reviewing themes and producing a report(205).

The main themes were found after repeated reading of the interview transcripts, paying careful attention to barriers and facilitators associated with the implementation of RBM in past, present and future clinical trials. Barriers were defined as perceived obstacles that would prevent or impact clinical researchers' implementation of RBM(208). Facilitators were defined as processes that would support RBM implementation(208). Emerging themes were organised hierarchically in three levels of analysis. At the first level are text relating to the barriers and facilitators associated with RBM implementation that that were identified across the data set. At the second level are the subthemes, where different codes were combined because they shared an underlying meaning. At the third level, are the main barriers and facilitators associated with the implementation of RBM.

4.3.4 Data Integration

The Good Reporting of a Mixed Methods Study (GRAMMS) framework was used to inform reporting of the findings(209). The survey and interview data were integrated at the data interpretation phase using the method of merging data(210). Merging occurs when researchers bring two data bases together for analysis and comparison(210). In this study, the research team conducted separate analyses of the quantitative survey data and the qualitative interview data in parallel. Qualitative information was used to explore quantitative information collected in Phase 1, as dictated by the explanatory sequential design(211).

4.3.5 Ethics

The study received ethical approval from the Research Ethics Committee of the Cork Teaching Hospitals (CREC). Informed consent was received from all study participants.

4.4 Results

4.4.1 Participant Characteristics and RBM uptake

The survey response rate was 49% (132/273). Characteristics of the survey participants are described in Table 9. Forty per cent of respondents were Principle Investigators (n=53). Most respondents had over 6 years' experience of working in clinical trials (57%, n=76) and over half had completed multi-centre and regulated trials (n=93, 70%).

Survey findings showed that 37% (n=49) of responders had conducted RBM since 2004. However, regardless of prior RBM experience, all survey participants said the Investigational Medicinal Product (IMP) under investigation, the phase of the clinical trial and the experience of the study team were the main factors they would use to determine how often a study monitor needed to visit a trial site to perform on-site monitoring. Survey responders reported several protocol deviations, or a high drop-out rate would warrant additional/triggered on-site monitoring.

In total, 24 survey respondents from four of the five CRF/Cs were invited to participate in the semi-structured interviews. Twenty-two interviews were conducted (RR=92%). Interview participants included PIs (n=6), nurses (n=5), monitors (n=3), study doctors (n=3), data managers (n=3), biostatistician (n=1) and trial pharmacist (n=1).

Table 9: Online survey participants' characteristics and use of clinical trial monitoring

Variable	Total (n=132)	%
Participants – clinical trial role		
▪ Principle Investigator (PI)	55	41%
▪ Clinical trial nurse	35	26%
▪ Project Manager	21	16%
▪ Quality Manager	4	3%
▪ Study doctor	5	4%
▪ Monitor	5	4%
▪ Biostatistics	2	1%
▪ Pharmacists	6	5%
Types of clinical trials conducted by participants		
▪ Industry	60	45%
▪ Academic	60	45%
▪ Non-regulatory	32	24%
Clinical trial experience (years)		
▪ <1	5	4%

▪ 1 – 3	37	28%%
▪ 4- 6	14	11%
▪ >6	76	51%
Conducted multi-centre clinical trial		
▪ Yes	86	64%
▪ N*o*	34	25%

4.4.2 Barriers associated with the implementation of RBM

4.4.2.1 Lack of knowledge /training

The survey results showed that 14% (*n* = 18) of responders were not familiar with the term RBM. Of the participants who did not conduct a risk assessment in the most recent clinical trial that they worked on (*n* = 35), 17% felt that they did not have the expertise to perform a risk assessment (Table 10). Over 80% (*n* = 114) of survey responders categorised barriers to implementing centralised monitoring. Almost two thirds of these participants (62%, *n* = 71) identified lack of education as a very important barrier (Table 11). The interview data confirmed that several participants had not used RBM in past trials because they were not familiar with this type of monitoring and many did not know that RBM would be introduced in the new ICH-GCP guideline:

> 'Well, just from talking to yourself, I have to admit, prior to that I hadn't heard about this, so I wasn't aware that the GCP was going to be changing' (Study physician-1).

Several interviewees, who had not conducted RBM in past trials, felt that they did not have enough RBM training to confidently perform RBM in future trials:

> 'It would come down to the practical aspects on how is risk defined …what information are people using to make that judgement. How is it a clinical trial implemented? But ultimately I'd have to understand that before I could say I was happy to do it' (PI-1).

They did not feel able to classify clinical trial risks and to translate these risks into monitoring activity. Similarly, some interviewees who had conducted RBM in past trials still felt ill-equipped to perform RBM in their future trials:

> 'We would say we have conducted a type of risk-based monitoring, but it's getting to the nitty-gritty of exactly what fields you're going to look at and exactly what parameters are in those fields. I would say that I'd be still a bit unsure of that' (Nurse-1).

Survey responders reported having limited experience of using centralized monitoring for essential monitoring activity such as assessing protocol compliance, inspecting informed consent and recording pharmacovigilance information. Lack of education was the main reason that survey participants did not perform centralized monitoring (Table 11). A small number of participants from the five CRF/Cs (*n* = 17) reported having a Standard Operating Procedure (SOP) for centralized monitoring in their CRF/C. However, over a third of participants (*n* = 48) were unsure if such a SOP existed in their CRF/C. Analysis of the qualitative interviews showed that some study nurses and monitors did not know how centralized monitoring could replace on-site monitoring. One participant felt that on-site monitoring offered better governance of junior clinical trial staff. This participant also felt that centralized monitoring would result in monitors having less oversight of clinical trial activity:

> 'As sponsor, all of the monitoring is on-site, and that's for two reasons…, because it's our first time working with a lot of these investigators and we're not sure of their experience in running regulated trials, we want to make sure that they understand what's required and what they need to do in terms of quality' (Monitor-2).

4.4.2.2 Increased cost caused by greater Information Technology (IT) demands

Almost half the survey responders identified IT demands (46%, *n* = 53) and cost (40%, *n* = 45) as problems associated with the implementation of centralized monitoring in past and future clinical trials (Table 11). The interview data revealed that this

perception was related to higher costs associated with EDC systems. Some interviewees felt that centralized monitoring would be costly to run as they would have to store trial data on an EDC system:

> 'As sponsor, all of the monitoring is on-site…, because we don't have electronic data capture in any of these studies because they're not commercial studies – they're usually grant funded, or just the PI – so there's very little money, you're using paper CRF'. (Monitor-1).

This was a particular concern for trialists working on smaller trials. They felt that their organizations would not have sufficient budget to support an EDC system and were only resourced to conduct on-site monitoring:

> 'Some of the eCRFs, let's say that company that we had, you could be talking nearly half a million, a million to get it up and running, and what small study has that if you're talking about an oncology study which has maybe 10 patients coming into it? An eCRF is not going to be worth the set-up costs. So they'll stick to the paper' (Monitor-3).

4.4.2.3 Increased work load

Survey findings showed that perceived work load was the main reason why responders did not conduct a risk assessment prior to developing the monitoring plan for their most recent trial (Table 10). Forty-one percent of survey responders (*n* = 114) thought that increased workload was a barrier associated with the implementation of centralized monitoring (Table 11). Interviewees, who had previously conducted centralized monitoring, felt that it resulted in more administration work for trial sites as they had to support trial monitors by scanning and uploading site documents to EDC systems:

> 'I noticed one of the girls downstairs was saying in the last couple of weeks… this company kept saying, "We still don't have the CV," and she'd sent it three times to them. So you need to have good people at the other side doing the

monitoring and stuff like that. It's just if it's maybe stuff from the trial master file that they're not here checking and consent forms and that. That probably might add some work' (Nurse-3).

Some interview participants felt that sponsors would use RBM as an excuse to perform less on-site monitoring and more remote monitoring. These participants felt that a reduction in on-site visits would results in a trial monitors spending less time on site checking trial documentation such as patient Consent Forms. These participants felt that study nurses may be expected to do extra administration tasks to support trial monitors perform remote monitoring:

'They have these centralized systems now where everything is stored centrally and it's, like, "Logon and you'll find the latest version of your protocol". So you have to complete training for that system, you have to logon every time the new protocol is available or whatever. The onus is on the site to print it off. The onus is on the site to do everything and it's just more and more it's on the site, and we are not paid adequately for everything that we are being requested to do. It's our admin staff as well. It's like they're just working for the pharma companies. There's just a huge amount of resources, and it's not accounted for' (Nurse-4).

4.4.2.4 Lack of verification

The survey found that 27% (*n* = 35) of responders did not conduct a risk assessment prior to developing the monitoring plan for their most recent clinical trial. Some participants did not conduct a risk assessment because they felt that it was not a GCP requirement and would not improve patient safety (Table 10). However, these participants did use an informal process to determine what level of on-site monitoring was required for their clinical trial. Also, 21% of survey responders (*n* = 28) reported previous RBM experience.

Interview analysis showed that participants perceived a lack of scientific evidence supporting RBM and saw this as a potential barrier to its implementation in their

future clinical trials. Many felt that enough proof did not exist to confirm that RBM was at least as effective and efficient as the 100% SDV on-site monitoring process that they currently used:

> 'So it's just our experience that the more frequent the monitoring the better. I have a negative attitude towards already a negative perception of the risk-based monitoring because 100% source data verification is what I would prefer' (Nurse-1).

Some interviewees believed that RBM would lead to a greater reliance on centralized monitoring and a move away from on-site monitoring:

> 'I know the new ICH-GCP guideline are more into the technology, and I know that's the way we're going and things like that. At the end of the day, I don't think it fully replaces the on-site' (Nurse-2).

Many felt that the merits of centralized monitoring had yet to be proven and so were not comfortable conducting RBM in future trials if it meant fewer on-site visits:

> 'I suppose the fact that things are going more electronic and it is more EDC-based. It's the management of stuff that cannot be converted into EDC and how that's going to be verified and how that's going to be monitored' (Monitor-1).

Table 10: Reasons why survey responders did or did not conduct a risk assessment prior to developing the monitoring plan

Facilitators	%	Barriers	%
To improve patient safety	43 (88%)	Question not relevant, developing monitoring plan is a Sponsor duty	15 (47%)
To improve data accuracy	32 (65%)	Not sure	9 (28%)
To fulfil GCP requirements	29 (59%)	It is not a GCP requirement	7 (22%)
To determine a schedule for on-site monitoring visits	21 (43%)	Do not have the expertise to perform a risk assessment	6 (19%)

To fulfil HPRA/IMB requirements	20 (41%)	It is too time consuming	6 (19%)
To reduce monitoring costs	8 (16%)	It will not improve patient safety	2 (6%)
Not sure	3 (6%)	It is too expensive	1 (3%)

Table 11: Perceived problems associated with the implementation of centralised Monitoring (n=114)

Factor	Yes	No	Not sure
Lack of education and training in centralised monitoring	71 (62%)	36 (31%)	8 (7%)
Cost associated with centralised monitoring	45 (40%)	54 (48%)	13 (12%)
IT demands of centralised monitoring	53 (46%)	53 (46%)	9 (8%)
Workload associated with centralised monitoring	47 (42%)	48 (16%)	18 (16%)

4.4.3 Facilitators

4.4.3.1 Necessary requirement/mandate

Compliance with GCP was the main criterion participants considered when selecting a RBM tool. Of the 35 survey responders who did not conduct a risk assessment of their most recent monitoring, 20% (*n* = 7) of these participants attributed this to the absence of a GCP requirement to do so (Table 10). Correspondingly, the interview data confirmed that fulfilling GCP requirements would now motivate them to conduct RBM in future trials:

> 'Yes, we will because it will be ICH-GCP will require us to do so' (Monitor-3).

Several interview participants said that adapting monitoring to the level of risk was a justified addition to ICH-GCP:

> ‘It does make sense that there’s some degree difference of risk, and therefore that the regulator environment would recognise that’ (PI-2).

They viewed the new requirements positively because they felt that RBM was a more sustainable approach to monitoring than existing approaches:

> ‘The landscape of clinical research has been changing, and is always changing, and just changes, changes… It is inevitable because the days of 100% source data verification is just not sustainable, really. But yeah, no, we’re definitely going to go down that route, so we are, when we get ourselves together. You know, we get more experienced, and get a bit of training’ (PI-4).

Similarly, several participants said that they would implement RBM if it became a funding or publication requirement:

> ‘People will put it into practice if it helps them to get funded or it helps them to publish their work’ (Biostatistician-1).

4.4.3.2 Availability of, and need for, guidance

Survey results suggest that more regulatory guidance would have facilitated the use of RBM in past trials (Table 10). Similarly, most interview participants believed that the introduction of regulatory-endorsed guideline would facilitate the implementation of RBM. In Ireland, clinical trials are regulated by the Health Protection Regulatory Authorities (HPRA) and some participants suggested that this organisation should lead the way in RBM implementation:

‘I think it would be very important to have the HPRA involved, because, as you know, they come and monitor our studies’ (Monitor-3).

‘Well, somebody from the HPRA. There need to be quality and regulatory affairs. Managers involved and stuff like that. HPRA maybe’ (Nurse-5).

Some participants thought that RBM would result in more efficient monitoring because monitoring activity would be based solely on the risk classification of each individual trial:

> 'I think it would be useful in making sure that wastage saved, that there was proper scrutiny of patients in the study. It's a robust means of recording data, and probably having expert, external review of any adverse events' (PI-5).

4.4.3.3 Economic benefits

Perceived financial benefit of RBM served as another facilitator encouraging interview participants to perform RBM in their future trials. Participants felt that RBM could reduce trial expenditure because monitoring activity would only be done as required:

> 'But I think it is more cost-effective as well and I think that is an advantage' (Quality manager-1).

Some interviewees believed that RBM would lead to a reduction in the number of on-site visits that would be performed by a monitor in each trial. These participants thought that reduced on-site monitoring visits would lead to an overall reduction in trial expenditure on monitoring:

> 'So there clearly are benefits. The first one is to the extent that you're able to replace on-site monitoring with risk-based monitoring. You have achieved a cost saving for the sponsor of the study' (Nurse-5).

4.5 Discussion

As far as we are aware, this is the first mixed methods study to investigate the perceived barriers and facilitators to RBM in academic-led clinical trials. Our survey showed that over one-third of respondents had previously performed RBM. The ICH-GCP Integrated Addendum will come into effect on the 14th of June 2017 so the proportion of clinical researchers performing RBM is likely to rise in the future.

However, the survey results show that currently the majority of staff in academic CRF/Cs have no experience of performing RBM. Our qualitative analysis found a lack of RBM verification as one of the main barriers preventing interview participants from performing RBM. Most interviewees said that they would feel uncomfortable conducting RBM as they believed its effectiveness had yet to be proven. Some participants felt that RBM may reduce the quality of clinical trial monitoring by offering a less intensive monitoring approach compared to traditional 100% on-site SDV. These concerns are well founded as scientific evidence confirming the effectiveness and efficiency of RBM is sparse (29). To date, results from the OPTIMON trial are the only ones that compare RBM to traditional 100% on-site SDV monitoring. Of note, this study lacked sufficient statistical power to demonstrate non-inferiority of the RBM approach at detecting errors in the participant consent process, notification of serious adverse events (SAEs) and incorrect application of participant's eligibility criteria(143). Thus, data supporting the safety and effectiveness of RBM are much needed(146). However, irrespective of this evidence gap, to be ICH-GCP compliant clinical researchers must implement RBM in their future trials (146, 212).

Our study highlighted three additional barriers that may inhibit the introduction of RBM into academic-led clinical trial units. These included lack of RBM knowledge/training, perceived risk of increased costs caused by greater IT demands and perceived risk of increased workload for trial staff. Lack of RBM knowledge/training was identified as a major obstacle to RBM implementation among interview participants. Many felt ill-equipped to perform the initial risk assessment phase of the RBM process. This finding was reflected in the survey results, which revealed that less than one third of responders had performed a risk assessment prior to developing the monitoring plan for their most recent clinical trial. Also, the use of risk assessment among our study population was much lower than the 87% uptake recorded among American academic clinical trialists in 2011 (203). The low uptake of risk assessment among our study participants is a cause for concern. Under the new ICH-GCP guideline, sponsors must base their monitoring plans on the results of a risk assessment of their trial protocol (23). Therefore, in Ireland, the knowledge gap surrounding risk assessment must be addressed if

academic trialists are to become proficient RBM practitioners (146). Interviewees believed that the availability of regulatory-endorsed guideline would facilitate the introduction of RBM into their academic-led clinical trial organizations. To increase the use of risk assessments, Irish clinical trial regulators should develop or select an approved RBM tool at a national level (170). A RBM tool would provide formal instruction on how to perform a risk assessment of a clinical trial protocol (10). Clinical trial regulators in the United Kingdom and France have already developed their own RBM tools (28, 31). Additionally, in 2014, Switzerland became the first European country to introduce a regulation adopting risk-based categorization into their clinical trial methodology(146). Consequently, a new article added to the Swiss Federal Constitution, provided the legal framework to regulate human research according to the risk to which participants are exposed(146). However, it must be noted that in Switzerland the structured risk categorization approach was not better than an ad-hoc risk assessment approach (146). Therefore, a RBM tool should only be used to guide risk assessment and not as a one-size-fits-all approach.

Survey findings suggest that participants are not yet equipped to perform centralised monitoring. Participants had limited experience of performing essential monitoring activity, such as inspecting informed consent and protocol compliance, through centralized monitoring. This is worrying as centralized monitoring is a primary component of RBM. As outlined in the new ICH-GCP guideline, sponsors should use centralized monitoring, it should be used to complement and reduce the extent and/or frequency of on-site monitoring (23). The perception of centralized monitoring was explored further in the qualitative phase of this study. Interview analysis showed that some participants believed that centralized monitoring would be costly to run as they would have to store trial data on an EDC system. Participants who worked on small academic trials thought that they would have insufficient budgets to support an EDC system and so they could only conduct on-site monitoring. The practical challenges associated with centralized monitoring will impact the implementation of RBM in Ireland because centralized monitoring is a major component of RBM(26, 134). If researchers do not have the resources to perform centralized monitoring, then in turn they will not be able to perform RBM as their

only option is to mitigate every clinical trial risk through on-site monitoring. Research is needed to develop pragmatic solutions to the challenges surrounding the use of centralized monitoring (20). In 2016, the Food and Drug Administration (FDA) signed an Agreement with CluePoints to explore and develop a data-driven centralized monitoring approach in clinical trials(213). CluePoints is an IT company that offers cloud-based RBM software. Following the FDA lead, it may be useful for other countries to develop a national SOP for centralized monitoring(213). This may involve collaboration between academic clinical researchers and computer programmers who specialize in RBM systems.

Conclusion

The results of this study confirm the absence of, and the need for, training and the availability of regulatory-endorsed guidelines to support the implementation of RBM in academic-led clinical trials. The results of this study should be used to inform interventions and strategies by policy-makers and clinical trial regulators to improve RBM uptake.

Strengths/limitations

To our knowledge, this is the first mixed-methods study to focus specifically on the barriers and facilitators associated with clinical researcher's implementation of RBM in academic-led clinical trials. The triangulation of the data enabled the in-depth examination of our findings, providing a deeper understanding of the influences at work and corroborating the interpretation of the data. This approach improves the validity of the data and increases its comprehensiveness (211). In addition our study was reported in accordance with Good Reporting of a Mixed Methods Study (GRAMMS) framework (209).

We believe that the results of this study are generalizable to the global academic clinical trial community that operates under ICH-GCP guideline. Our study included a sample of all researchers who would typically work on a clinical trial in an academic setting. These include PIs, nurses, physicians, monitors, pharmacists, managers and

biostatisticians (23). Our diverse study population allowed for the collection of data from all types of clinical trial staff and this increased our understanding of how RBM will be implemented into a real clinical trial setting (29).

However, our study does have some limitations. The study was cross-sectional which meant that estimates of RBM implementation could only be assessed at the present time point(214). The study used a mixed-methods, explanatory sequential design, with a quantitative and qualitative component. This type of study is inherently more challenging than a single-method study design as it involves the design, conduct and data integration of two different sources (215). Achieving true integration in a mixed-methods study can be difficult(215). To overcome this barrier, our study used the process of 'merging' to accurately link and analyze the quantitative and qualitative data(216). Integration through merging of data occurs when researchers bring the two databases together for analysis and for comparison(216). In the design phase, a plan was developed for collecting the quantitative and qualitative data that was conducive to merging the databases(216). Accordingly, the quantitative survey contained a series of questions pertaining to RBM that were like the questions included in the semi- structured interviews.

It should also be noted that our study was conducted before the new ICH-GCP guideline come into effect on 14 June 2017(212). A longitudinal study would allow us to track RBM uptake over time and explore its impact on clinical trial conduct and monitoring outcomes. Such a study could use the quantitative results of this study as baseline data. The response rate for the survey was 49% and, therefore, responses may represent a biased sample and may not be fully representative of all academic clinical researchers working in Irish CRF/Cs. Furthermore, the response rate for the qualitative phase of our study was 92%. The high response rate may be due to sampling bias(217). Finally, the qualitative phase of our study used two forms of data collection, face-to-face interviews and telephone interviews. We are confident that this did not impact the qualitative findings as there were no differences apparent in the data generated by both collection methods. This observation is in line with other

research which found no significant differences in the data generated by face-to-face and telephone interviews(218).

Chapter 5. On-site and centralised monitoring – the TRUST study experience

5.1 Abstract

The second version of the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines (GCP) recommends risk-based monitoring (RBM) for clinical trials of an Investigational Medicinal Product. RBM requires a combination of on-site and centralized monitoring. GCP does not specify which clinical trial activity should be performed on-site or centrally. In the absence of a gold standard approach, it is challenging for researchers to develop monitoring plans for their clinical trials that incorporate on-site and centralized monitoring and fulfill GCP's seventeen recommended monitoring activities. This document analysis is the first such study of on-site and centralised monitoring reports collected prospectively in an international multi-centre clinical trial, the TRUST study. It provides support for the use of RBM through a combination of on-site and centralised monitoring practices.

5.2 Introduction

In June 2017, the ICH published the revised ICH GCP guideline for clinical trial conduct (11). Under ICH GCP, sponsors in America, China and Europe are legally obliged to monitor clinical trial activity(11). ICH GCP recommends seventeen recommended monitoring activities (Table 14) for all Clinical Trials of an Investigational Medicinal Product (CTIMP). These monitoring activities include verifying protocol compliance, confirming IMP is correctly managed, ensuring trial staff are adequately trained, reporting participant recruitment rates and checking that participants have given informed consent (11). ICH GCP recommends that risk-based monitoring (RBM) should be used to complete these monitoring activities (126).

RBM has two sequential phases (10). First, the trial team must assess the risks in their study (10). Such risks relate to the IMP, study population and research team's experience (26, 133). Secondly, when the risks have been identified, the trial team must decide whether to monitor these risks through on-site (at the trial site) or centralised (remote evaluation of electronically captured trial data) monitoring; or both (10, 26). Centralized monitoring is the remote evaluation of the study data, carried out by a team including central monitors, medical reviewers at a location

other than the sites at which the clinical trial is being conducted (26). It is claimed that centralized monitoring can provide many of the capabilities of on-site monitoring as well as additional capabilities such as providing a cost efficient and data driven monitoring strategy(21, 46). Despite these claims, many trialists are reluctant to use centralised monitoring as they fear it may not be as good as on-site monitoring at detected errors and some believe they do not have the expertise or knowledge needed to perform centralised monitoring (29, 219)

However, the new ICH GCP guideline does not specify what monitoring activities should be performed on site or centrally (132, 219). Furthermore, there is no published research comparing the effectiveness of on-site and centralised monitoring in a trial (20). In the absence of evidence-based guidelines for clinical trial monitoring, trialists are unsure how to develop RBM plans that incorporate both on-site and centralised monitoring and fulfill ICH GCP's seventeen recommended monitoring activities (219).Until now, other studies in this area have only retrospectively compared monitoring practices by testing if findings from on-site monitoring could have been identified through centralized monitoring (119, 213). The findings of these studies suggest that in theory centralized monitoring could have detected the same findings as on-site monitoring (20). However, no study has compared on-site, and centralized monitoring activity conducted prospectively in a clinical trial.

We recently conducted a Study Within a Trial (SWAT) to provide the first document analysis of on-site and centralised monitoring reports collected prospectively in an international multi-centre clinical trial – the Thyroid Hormone Replacement for Subclinical Hypo-Thyroidism Trial (TRUST study) (149, 220).The TRUST study, was a randomised, multi-centre, phase III clinical trial, that compared thyroxin replacement to placebo (65). The study recruited participants from four European sites. Each site had the same frequency of centralised monitoring, but individual on-site monitoring plans were developed to manage local trial activity. The aim of the SWAT was to review the monitoring reports generated for the TRUST study to determine if on-site and centralised monitoring used simultaneously in a clinical trial, perform the same monitoring activities. This chapter reports the findings.

5.3 Methods

5.3.1 SWAT context

A Study within a Trial (SWAT) is a self-contained research study that has been embedded within a host trial with the aim of evaluating or exploring alternative ways of delivering or organising a trial process. SWATs evaluate alternative ways of doing a trial process (e.g. recruiting patients, helping them to stay in the study, or reporting the findings) to provide evidence about how to improve the process.This SWAT was embedded within the TRUST study, a randomised, multi-centre, phase III clinical trial (149, 221), that compared thyroxin replacement to placebo in 738 community dwelling adults aged ≥65 years with subclinical hypothyroidism (SCH). The trial was conducted over three-and-a-half years from 2013-2017 (221). It had recruiting sites in four EU countries (UK, Netherlands, Ireland and Switzerland) (221).

The SWAT protocol (SWAT number 38) is registered on the SWAT Repository Store managed by the Northern Ireland Hub for Trials Methodology Research(222).

5.3.2 Study -Design

This SWAT used a deductive qualitative document analysis approach to compare on-site and centralised monitoring reports from the TRUST study.

5.3.3 Study - Sample and data collection

5.3.3.1 Data source

All on-site and centralised monitoring reports generated by the trial's four recruiting sites. TRUST participants had four in-person visits and one telephone contact over a minimum 1-year follow-up period(221). Data generated from these visits or telephone call were entered into an electronic case report form (eCRF)(220). The eCRF data were managed, monitored and analysed centrally by the Robertson Centre for Biostatistics in Glasgow. Each site had the same frequency of centralised monitoring. In addition, research staff at each site devised their individual on-site monitoring plan to manage local trial activity.

5.3.3.2 On-site monitoring

In total, 29 on-site monitoring reports were analysed (Table 12). On-site monitoring reports included:

1) pre-trial monitoring reports (n=3) that verified the sites suitability to conduct the trial

2) trial initiation monitoring reports (n=2), confirming trial procedures were adequate for the trial to start

3) trial monitoring reports (n=20), documenting routine monitoring visits during the trial and

4) final close out monitoring reports (n=4), checking all close out activities (such as data archiving)were completed before the trial ended (126).

5.3.3.3 Centralised monitoring

We have defined centralised monitoring as the generation of eCRF data queries. These data queries were either automatic or manual. Automatic data queries were raised if data entered into the eCRF did not comply with pre-specified validation rules such as participant inclusion criteria (Appendix D). A manual data query was raised when random eCRF checks identified data errors (Appendix D). Identification of an automatic or manual data query resulted in the Robertson Centre sending an email to the relevant trial site requesting correction or clarification of the data entry (Figure 8). In total 1,825 data queries were raised, and all queries were analyzed for this report (Table 12).

Figure 7: Data query process

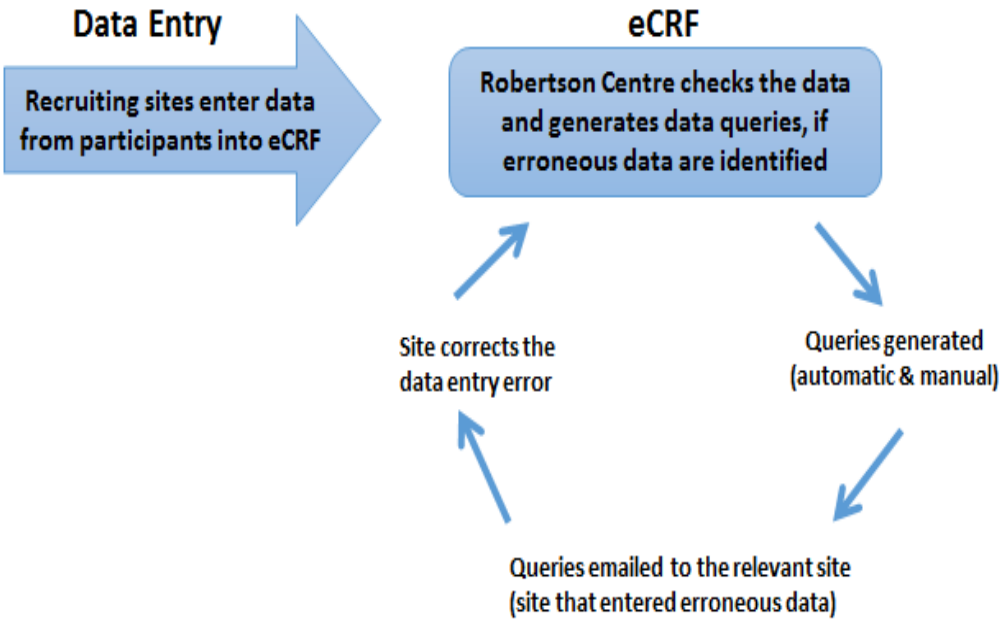


Table 12: Summary of on-site monitoring reports and centralised monitoring (data queries)

On-site monitoring					Centralised monitoring	
Site	**Pre-trial monitoring report visit (n=3)**	**Trial initiation monitoring report (n=2)**	**Trial monitoring visits reports (n=20)**	**Close-out monitoring reports (n=4)**	**Automatic data queries (n=1335)**	**Manual data queries (n=490)**
Site 1	1	1	9	1	503	74
Site 2	0	1	3	1	267	152
Site 3	1	0	3	1	206	103
Site 4	1	0	5	1	359	161

5.3.4 Data Analysis

Two researchers (CH and MZ) independently analyzed all monitoring reports using deductive document analysis. The data analysis consisted of four phases: decontextualisation; recontextualisation; categorisation; **and** compilation *(223)*. These are described in Table 13.

Table 13: Four phases of deductive document analysis

Phase	Purpose
1. Decontextualisation	CH and MZ independently read through the monitoring reports three times to familiarize themselves with the data. The data were then reduced to potential meaning units using highlighted text (223). A meaning unit was defined as the smallest piece of text from a monitoring report data that related to at least one of ICH GCP's seventeen recommended monitoring activity (Table 14).
2. Recontextualisation	CH and MZ compared the potential meaning units to identify 'actual' meaning units that they agreed fulfilled at least one of ICH GCP's seventeen recommended monitoring activities. Next, CH and MZ re-read the

	monitoring reports alongside the final list of 'actual' meaning units. After this process was performed, unmarked text in each monitoring report that did not relate to a meaning unit was excluded.
3. Categorisation	CH and MZ independently condensed meaning units into pre-defined categories based on ICH GCP's seventeen recommended monitoring activities.
4. Compilation	CH and MZ compared results and reached consensus on all meaning units. Each meaning unit was then dichotomized into a yes or no variable (Table 14).

The **Yes** variable was defined as a meaning unit that showed an ICH GCP monitoring activity had been achieved through on-site or centralised monitoring (Table 14). For centralised monitoring, the results were combined for all four recruiting sites because each site received the same frequency and types of centralised monitoring (see section 5.3.3). The **No** variable was defined as an ICH GCP monitoring activity that was not described in the monitoring report.

5.3.5 Ethical approval

This study involves the secondary analysis of data collected for the TRUST study. TRUST received full ethical and regulatory approval from the relevant bodies in each of the four recruiting countries. The TRUST Thyroid Trial publication committee approved this SWAT.

5.4. Results

The Results section is presented in accordance with the two primary components of deduction analysis that was discussed in detail in section 5.3.2. These components are the identification of meaning units and the application of the meaning units to the pre-defined ICH GCP monitoring activity.

5.4.1. Identification of meaning units

For this study, a meaning unit was defined as a finding reported in the on-site and centralized monitoring reports (automatic and manual queries) that related to at least one of the ICH GCP's seventeen recommended monitoring activity.

5.4.1.1 Meaning units derived from on-site monitoring reports (n=29).

Two researchers (CH & MZ) reviewed the on-site monitoring reports for each of the four trial sites and identified meaning units that they agreed related at least one of GCP's seventeen recommended monitoring activities (Table 14). The researchers identified evidence in the on-site monitoring reports that showed at least one of the four sites had used on-site monitoring to implement (completely or partially) sixteen of GCP's recommended monitoring activity. For example, if the on-site monitoring report commented on the presence of the trial team's signed and dated Curriculum Vitae in the Investigational Site File, this information was converted into a meaning unit that confirmed GCP recommended monitoring activity 2 (*verifying the investigator has adequate qualifications and resources to complete the trial*) was fulfilled through on-site monitoring. A meaning unit for GCP recommended monitoring activity 6-*Verifying that written informed consent was obtained before each subject's participation in the trial*' was identified from findings included in the monitoring report that confirmed the monitor had checked that informed consent was provided by all participants that were enrolled into the trial. However, the researchers did not identify text in the on-site monitoring reports, for the four sites, that provided evidence to suggest on- site monitoring was a main line of communication between the sponsor and the investigator (GCP recommended monitoring activity 1).

Table 14 : Meaning units identified from on-site monitoring reports

ICH GCP monitoring activity	**Site A** (12 monitoring reports)	**Site B** (5 monitoring reports)	**Site C** (5 monitoring reports)	**Site D** (7 monitoring reports)
1. Acting as the main line of communication between the sponsor and the investigator.	**No** evidence present in the on-site monitoring reports to confirm this activity	**No** evidence present in the on-site monitoring reports to confirm this activity	**No** evidence present in the on-site monitoring reports to confirm this activity	**No** evidence present in the on-site monitoring reports to confirm this activity
2. Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.	**Yes** – in the monitoring reports the monitor repots on the presence of the trial team's signed and dated CVs in the Investigational Site File	**Yes** – in the on-site monitoring report it states that the team's CVs and GCP certificates are present in up to date.	**No** evidence in the reports to suggest this activity was performed through on-site monitoring	**Yes** – in the monitoring reports the monitor repots on the presence of the trial team's signed and dated CVs in the Investigational Site File
3. Verifying, for the investigational product(s) (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.	**Yes- the** monitoring report includes findings from assessing the storage and supply of the investigational produce which was	**Yes** – all the activities (I –v) were assessed and findings reported in the close out monitoring visit.	**Yes** – the monitoring report states that the "complete and accurate accountability records for study medication was kept" and that the	Yes – the monitoring reports discusses the review of the 'accountability log' which shows how the

(ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s). (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s). (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately. (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor	documented in the Pharmacy site file.		study medication as properly stored.	medication was stored and dispensed. In the close out monitoring visit, the monitor included findings referring to how patients returned unused medication to the trial site and then destroyed by the pharmacy.
4. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.	**Yes** – in the monitoring reports it states that all protocol deviations were assessed, and recommendations assigned to ensure	**Yes** – in the monitoring reports it states that all protocol deviations were assessed, and recommendations assigned to ensure	**Yes** – in the monitoring reports it states that all protocol deviations were assessed, and recommendations assigned to ensure	**Yes** – in the monitoring reports it states that all protocol deviations were assessed, and recommendations assigned to ensure

	outstanding deviations were completed.	outstanding deviations were completed.	outstanding deviations were completed.	outstanding deviations were completed.
5. Verifying that written informed consent was obtained before each subject's participation in the trial.	**Yes** – the monitoring reports checked and states that informed consent was provided by all participants enrolled into the trial.	**Yes** – the monitoring reports checked and states that informed consent was provided by all participants enrolled into the trial.	**Yes** – the monitoring reports checked and states that informed consent was provided by all participants enrolled into the trial.	**Yes** – the monitoring reports checked and states that informed consent was provided by all participants enrolled into the trial.
6. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).	**Yes**- Trial Master File reviewed during on-site visit and findings included in the monitoring report	**Yes**- Trial Master File reviewed during on-site visit and findings included in the monitoring report	**Yes**- Trial Master File reviewed during on-site visit and findings included in the monitoring report	No – no information included in the monitoring reports to suggest the Trial Master File or the Site Master File was reviewed during the on-site visits
7. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.	**Yes**- delegation log available and signed by all staff	**Yes**- delegation log available and signed by all staff	**Yes**- delegation log available and signed by all staff	**Yes**- delegation log available and signed by all staff
8. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor	**Yes**- delegation log available and signed by all staff	**Yes**- delegation log available and signed by all staff	**Yes**- delegation log available and signed by all staff	**Yes**- delegation log available and signed by all staff

and the investigator/institution and have not delegated these functions to unauthorized individuals.				
9. Verifying that the investigator is enrolling only eligible subjects	**Yes** – the monitoring report states that the eligible of study participants was assessed during the on-site visit	**Yes** – the monitoring report states that the eligible of study participants was assessed during the on-site visit	**Yes** – the monitoring report states that the eligible of study participants was assessed during the on-site visit	**Yes** – the monitoring report states that the eligible of study participants was assessed during the on-site visit
10. Reporting the subject recruitment rate.	**Yes-** the number of participants enrolled in the trial is documented in the monitoring report	**No** – the recruitment rate or even the overall number of participants enrolled in the trial was not documented in the monitoring report	**No** – the recruitment rate or even the overall number of participants enrolled in the trial was not documented in the monitoring report	**Yes-** the number of participants enrolled in the trial is documented in the monitoring report
11. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.	**Yes**- source documented such as laboratory reports and participant questionnaires were reviewed during the on-site visit	**Yes**- source documented such as laboratory reports were reviewed during the on-site visit	**Yes**- source documented such as patient report forms were reviewed during the on-site visit	**Yes**- source documented such as laboratory reports and participant questionnaires were reviewed during the on-site visit

12. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.	**Yes** – evidence provided in the monitoring report that the application and approval for protocol amendments and ethic submissions were regularly performed by the investigator	**Yes** – evidence provided in the monitoring report that the application and approval for protocol amendments and ethic submissions were regularly performed by the investigator	**Yes** – evidence provided in the monitoring report that the application and approval for protocol amendments and ethic submissions were regularly performed by the investigator	**Yes** – evidence provided in the monitoring report that the application and approval for protocol amendments and ethic submissions were regularly performed by the investigator
13. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that: (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents. (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects. (iii) Adverse events, concomitant medications and intercurrent illnesses	**Yes** – patient case report forms were reviewed during and findings included in the on-site monitoring reports. **Yes** – the on-site report includes the number and brief description of SAEs and resolution action performed by the trial team	**Yes** – the on-site report includes the number and brief description of SAEs and resolution action performed by the trial team	**Yes** – the on-site report includes the number and brief description of SAEs and resolution action performed by the trial team	**Yes** – patient case report forms were reviewed during and findings included in the on-site monitoring reports. **Yes** – the on-site report includes the number and brief description of SAEs and resolution action performed by the trial team

are reported in accordance with the protocol on the CRFs. (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs. (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.				
14. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.	**Yes** – the monitor report includes a recommendation for action required to correct errors in the CRF. The implementation of the recommendation is reviewed by the monitor at later on-site visits.	**Yes** – the monitor report includes a recommendation for action required to correct errors in the CRF. However, no evidence to suggest the implementation of the recommendations is later assessed.	**Yes** – the monitor report includes a recommendation for action required to correct errors in the CRF. The implementation of the recommendation is reviewed by the monitor at later on-site visits.	**Yes** – the monitor report includes a recommendation for action required to correct errors in the CRF. However, no evidence to suggest the implementation of the recommendations is later assessed.
15. Determining whether all adverse events (AEs) are appropriately reported within	**Yes** – the on-site report includes the number and brief description of	**Yes** – the on-site report includes the number and brief description of	**Yes** – the on-site report includes the number and brief description of	**Yes** – the on-site report includes the number and brief description of

the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).	SAEs and resolution action performed by the trial team	SAEs and resolution action performed by the trial team	SAEs and resolution action performed by the trial team	SAEs and resolution action performed by the trial team
16. Determining whether the investigator is maintaining the essential documents	**Yes**- Trial Master File reviewed during on-site visit and findings included in the monitoring report	**Yes**- Trial Master File reviewed during on-site visit and findings included in the monitoring report	**Yes**- Trial Master File reviewed during on-site visit and findings included in the monitoring report	No – no information included in the monitoring reports to suggest the Trial Master File or the Site Master File was reviewed during the on-site visits
17. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations	**Yes**- the monitoring report shows the number and brief description of all protocol deviations and action taken for their resolution	**Yes**- the monitoring report shows the number and brief description of all protocol deviations and action taken for their resolution	**Yes**- the monitoring report shows the number and brief description of all protocol deviations and action taken for their resolution	**Yes**- the monitoring report shows the number and brief description of all protocol deviations and action taken for their resolution

5.4.1.2 Meaning units identified from centralised monitoring reports (automatic and manual queries)

Table 15 shows the meaning units that were identified in the automatic and manual queries raised by the Robertson Centre for the four trial sites. Of the seventeen GCP recommended monitoring activities, meaning units could only be identified for eleven monitoring activities. For example, a meaning unit for GCP recommended monitoring activity 8, '*Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol',* was developing from automatic queries that were raised trial site's that had deviated from the approved protocol by not conducting participant's visits within the allocated time frame.

Table 15: Meaning units derived from centralised monitoring reports (automatic and manual queries).

GCP monitoring activity	**automatic and manual queries** (combined for all four trial sites)
1. Acting as the main line of communication between the sponsor and the investigator.	**No** evidence in the automatic and manual queries to suggest centralized monitoring was used as a line of communication
2. Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.	**No** evidence in the automatic and manual queries to suggest centralized monitoring was used to verify the investigator had adequate qualifications and resources to conduct the trial
3. Verifying, for the investigational product(s) that storage times and conditions are acceptable, and that supplies are sufficient throughout the trial. That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s). That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s). • **That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.**	**Yes -** manual queries raised regarding the supply of the Investigation Product to ineligible patients. Through review of the electronic Case Report Form (e CRF) a number of manual queries were raised regarded the supply of study medication to patients that were on 'prohibited medicine' as listed in the (e CRF)

• **That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor**	
4. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.	**Yes** - several automatic queries were raised for each site regarding protocol deviations For example, participants missing scheduled visits as outlined in the protocol.
5. Verifying that written informed consent was obtained before each subject's participation in the trial.	**No** - no evidence to suggest informed consent was checked through centralised monitoring
6. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).	**No** – no evidence to suggest this activity was performed through centralised monitoring
7. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.	**Yes –** the automatic and manual queries are raised in a timely manner and keep the investigators informed on the trial activity. For example - delays in entering participants blood test results into their e CRF
8. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution and have not delegated these functions to unauthorized individuals.	**Yes** – several automatic queries were raised for trial site's that had deviated from the approved protocol by not conducting participant's visits within the allocated time frame.
9. Verifying that the investigator is enrolling only eligible subjects	**Yes** - several manual queries raised for participants that reported taking concomitant medications in the e CRF. The manual query was raised asking the investigator to confirm the participant's eligibility to participate in the trial as this was a protocol deviation.
10. Reporting the subject recruitment rate.	**No** – no evidence to suggest this activity was performed through centralised monitoring
11. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.	**Yes** – all participant information was entered into an e CRF. Several automatic queries were raised for instances when the investigators had omitted participant data such as #last time the patient ate'.
12. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.	**Yes** – manual queries raised regarding the submission of outstanding SAE reports and laboratory reports.

13. . Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that: (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents. (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects. (iii) Adverse events, concomitant medications and illnesses are reported in accordance with protocol on the CRFs. (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs. (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs**.**	**Yes** – automatic queries were raised when an AE was reported for a patient, but no AE specialised interest forms was completed on the patients e CRF. The automatic queries requested the completion and submission of the AE form.
14. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.	**Yes** – all participant information was entered into an e CRF. Several automatic queries were raised for instances when the investigators had omitted participant data such as #last time the patient ate'.
15. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).	**Yes** – automatic queries were raised when an AE was reported for a patient, but no AE specialised interest forms was completed on the patients e CRF. The automatic queries requested the completion and submission of the AE form.
16. Determining whether the investigator is maintaining the essential documents	**No** – findings regarding essential documents such as the Site Files and patient informed consent forms were not raised through automatic or manual queries
17. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations	**Yes** - several manual queries raised for participants that reported taking concomitant medications in the e CRF. The manual query was raised asking the investigator to confirm the participant's eligibility to participate in the trial as this was a protocol deviation.

5.4.2 Application of the meaning units to identify of ICH GCP monitoring activity performed through on-site and centralised monitoring

Categorisation and compilation: condensed meaning units into pre-defined categories based on ICH GCP's seventeen recommended monitoring activities. Each meaning unit was then dichotomized into a yes or no variable and Results are outlined in Table 16.

5.4.2.1 On-site monitoring

The results presented in Table 16 show that none of the four recruiting sites achieved all of ICH GCP's seventeen monitoring activities through on-site monitoring. None of the sites appeared to have used on-site monitoring to complete GCP monitoring activity 1 – which was to confirm the monitor was '*Acting as the main line of communication between the sponsor and the investigator'.*

All four sites used on-site monitoring to complete eight of the GCP monitoring activities, 2, 3, 4, 5, 8, 9, 15 and 17 (Table 16). Sites B and C did not *'Report the subject recruitment* rate' (GCP monitoring activity 10) in their on-site monitoring reports. Site B was the only site that did not indicate completion of GCP monitoring activity 16, '*Determining whether the investigator is maintaining the essential documents'* in their on-site monitoring report. Site D was the only site that did not indicate that GCP monitoring activity 6 had been performed in their monitoring report- '*Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s)'.* On-site monitoring reports for Site C suggested that six GCP monitoring activity (2, 7, 10, 11, 12 and 14) had not been checked during on-site visits (Table 16).

5.4.2.2 Centralised monitoring

The four recruiting sites had the same frequency and type of centralised monitoring (Table 16). Ten of GCP's seventeen monitoring activities were completed through centralised monitoring (4, 7, 8, 9, 11, 12, 13, 14, 15 and 17). All ten activities

monitored centrally were also monitored through on-site monitoring at each of the four recruiting sites (Table 16). Six monitoring activities (1, 2, 5, 6, 10 and 16) were not reported in the centralised monitoring reports (Table 16).

Table 16: GCP monitoring requirement fulfilled through on site and centralised monitoring (automatic and manual queries)

ICH GCP monitoring activity	Site A		Site B		Site C		Site D	
	Onsite	Central	Onsite	Central	Onsite	Central	Onsite	Central
1. Acting as the main line of communication between the sponsor and the investigator.	No	No	No	No	No	No	No	No
2. Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.	Yes	No	Yes	No	No	No	Yes	No
3. Verifying, for the investigational product(s) (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial. (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s). (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s). (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately. (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Verifying that written informed consent was obtained before each subject's participation in the trial.	Yes	No	Yes	No	Yes	No	Yes	No
6. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies	Yes	No	Yes	No	Yes	No	No	No

needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).								
7. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
8. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution and have not delegated these functions to unauthorized individuals.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Verifying that the investigator is enrolling only eligible subjects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Reporting the subject recruitment rate.	Yes	No	No	No	No	No	Yes	No
11. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
12. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.	Yes	Yes	No	Yes	No	Yes	Yes	Yes
13. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that: (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents. (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects. (iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs. (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs. (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

14. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
15. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Determining whether the investigator is maintaining the essential documents	Yes	No	Yes	No	Yes	No	No	No
17. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

5.5 Discussion

The aim of the SWAT was to review the monitoring reports generated for the TRUST study to determine if on-site and centralised monitoring used simultaneously in this clinical trial, perform the same monitoring activities. To our knowledge, this is the first study to compare on-site activity centralised monitoring activity using data collected prospectively in a clinical trial. We found that on-site monitoring was used more frequently than centralised monitoring in the TRUST study. Sixteen of the seventeen recommended ICH GCP monitoring activities were completed through on-site visits. In contrast, only eleven of the seventeen recommended monitoring activities were completed through centralised monitoring (Table 16). This finding supports results from previous our study on the perspective of RBM in academic-led clinical trials (chapter 4), which showed that trialists favoured on-site monitoring over centralised monitoring (219). Trialists said they preferred on-site monitoring, as they felt they did not have the expertise needed to perform centralised monitoring (219).

The findings of the centralised monitoring activity performed in the TRUST study must be considered with caution. In accordance with the deductive document analysis methodology, two researchers analysed the automatic and manual queries to identify potential meaning units pertaining to GCP monitoring activity performed through centralised monitoring. As stated above, for centralized monitoring activity, meaning units could only be identified for eleven monitoring activities, from text included in the automatic and manual queries. However it must be noted that automatic and manual queries were only raised if a data entry error in a participant's eCRF was identified centrally by the Robertson Centre, who managed, monitored and analysed data entered into the trials Electronic Data Capture system. Therefore, the Robertson Centre may have been performing more centralised monitoring activity that was not fully apparent through our review of the automatic and manual queries. Furthermore, the on-site monitoring reports included in this study were not developed specifically for this SWAT and so they did not have a standardised the format. These reports differed in content, detail and length. Despite this limitation, the on-site monitoring reports still fulfilled the three quality criteria for documentary

evidence which are authenticity, credibility and comprehensiveness(224). The on-site monitoring reports were authentic documents from the TRUST Thyroid trial, they are credible monitoring reports typical of a clinical trial and all monitoring reports generated from the four TRUST sites were analysed in the document analysis.

The results of this research add to the evidence base for clinical trial monitoring and will help clinical researchers wishing to implement ICH GCP and move towards a system of diverse monitoring practices. Until now, other studies in this area have only retrospectively compared monitoring practices by testing if findings from on-site monitoring could have been identified centrally by adding specific data queries to the trial's EDC system (127, 225). These studies suggest critical on-site monitoring findings such as incorrect participant consent processes and inappropriate IMP dispensing, could have been identified through central monitoring techniques. However, the results of those studies are limited: both used arbitrary criteria to classify monitoring activity and neither reviewed all monitoring findings from a completed trial (127, 226). Our study is the first to compare on-site and centralised monitoring, during a completed trial, using ICH GCP guidelines.

This study showed all centralised monitoring activity was being completed through on-site monitoring which suggest on-site, and centralised monitoring are being used to complete the same recommended monitoring activities which could potentially lead to research wastage. This is an interesting finding as ICH GCP's emphasis on RBM is based on the assumption that on-site and centralised monitoring can be used together to prevent the waste of clinical trial resources (such as study budget and staff time) on monitoring activity that does not improve participant safety or data quality (24, 30, 131).

In recent years, many reports have been published claiming that centralised monitoring is more cost efficient and accurate than on-site monitoring. However, empirical data supporting these claims are lacking. On-site and centralised monitoring practices need to be evaluated empirically, including costs, to provide robust evidence for their contribution to trial performance and quality. From the four sites that participated in the TRUST study, there was twenty-nine on-site monitoring

reports created and over 1800 automatic and manual queries were raised through centralised monitoring. Further research is necessary to quantify and compare how much time, staff resources and trial budget is required to first perform but also to deal with the findings generated through on-site and centralised monitoring.

5.5.1 Strengths and Limitations

The study has several limitations that should be considered when interpreting the results. First the results of this study have been generated from a single clinical trial and may not be generalisable to other trials. Furthermore, the SWAT results are based on a document analysis and it is important to recognise the limitation of this method when drawing conclusions from a single data source reducing the validity and reliability of the study results (224). Document analysis is often used in combination with other qualitative research methods as a means of triangulation which allows for the combination of methodologies in the study of the same phenomenon. However, our study only included evidence from one data source; monitoring reports. Therefore, is was not possible to corroborate or converge our findings with other data sources such as interviews and observation with study monitors and the research team.

However, the study has many strengths. Firstly, our study used a SWAT design to answer a timely clinical trial methodology question, *'How should clinical trials be monitored using on-site and centralised monitoring?'*(149). Researchers and trialists face many uncertainties when designing and conducting research. Embedding a SWAT within a trial provides a cost-effective and practical way to answer these questions. Secondly, the monitoring reports analysed in this paper had already been generated as part of the TRUST Thyroid Trial. Therefore, these documents were non-reactive and unbiased as they were collected for another purpose(224). Finally, this is the first study to use prospective data to compare on-site and centralised monitoring. The results of this research will add to the evidence base for clinical trial monitoring(29).

Conclusion

This study provides an example of on-site and centralised monitoring activity performed simultaneously in a clinical trial. The results of the document analysis demonstrate a need for evidence-based guidelines to support the combined use of on-site and centralised monitoring in clinical trials.

Chapter 6. Introducing Risk-Based Monitoring tools into academic-led clinical trial units in Ireland: a quality improvement intervention

6.1 Abstract

Background

Risk based monitoring (RBM) tools provide comprehensive and structured RBM guidance. However, evidence supporting their usability is unknown and globally their usage among clinical researchers is low. The aim of this quality improvement (QI) study was to determine if a brief, educational, interactive, face to face workshop would result in increased use of RBM tools by academic clinical researchers in Ireland. Additionally, the study tested if RBM tool usability was linked to its use.

Methods

This QI intervention was developed by expert researchers and was conducted in four publicly funded academic run clinical trial units in Ireland. Each unit assembled a Multidisciplinary Testing Team (MDTT) comprised of members who normally develop, write, review and approve monitoring plans for trials managed in their clinical trial units. In total, the four MDTTs consisted of 12 participants; study doctor (n=1), quality and regulatory affair managers (n=4), clinical trial monitors (n=5) and research nurses (n=2). The usability of the RBM tools was assessed using the NASA Task Load questionnaire (NASA TLX) and the uptake of three RBM tool was measured using the Utilization Scale questionnaire.

Results

Three of the four MDTTS have implemented one of the three RBM tools in their clinical trial unit. All three RBM tools received a combined medium usability score for six dimensions of usability measured by the NASA TLX questionnaire; mental demand, physical demand, temporal demand, overall performance, frustration level and effort. At the six months follow up, results from the Utilization Scale questionnaire showed that three of the four MDTTs had taken steps or have fully implemented one of the three RBM tools into their clinical trial unit.

Conclusion

The findings of the study show that a brief, face to face, interactive education workshop is an effective way to encourage RBM tool usage. This study supports the global initiative aimed at increasing use of quality improvement interventions in clinical trials to improve clinical trial methodology.

6.2 Background

In June 2017, the revised International Conference on Harmonisation Good Clinical Practice (ICH GCP) guideline came into effect which endorsed risk-based monitoring (RBM)as best practice in clinical trial monitoring (23). RBM is a form of clinical trial monitoring (130). It incorporates both centralised monitoring, conducted off-site through an examination of electronic data, and on-site monitoring practices that are proportional to the risks associated with the clinical trial(23, 24). Further to the ICH GCP guidelines, the Organisation for Economic Co-operation and Development (OECD) has instructed clinical researchers to use a RBM tool when developing RBM plans (10). These tools have two functions: first, they support the pre-trial risk assessment of a clinical trial protocol and second, they provide guidance for subsequent on-site and/or centralised monitoring(10). Presently, RBM tools provide the most comprehensive and structured guidance for RBM implementation (10, 132). A systematic review I published in 2016, identified over twenty RBM tools that fulfil the OCED criteria. However, the usability of the RBM tools was not tested, this means the extent to which an RBM tool can be used by clinical researchers to conduct RBM with effectiveness, efficiency and satisfaction remains unknown (132, 227). To date, no gold standard RBM approach has been developed (129).

Despite the availability of ICH GCP guidelines and RBM tools, challenges still exist with respect to clinical researchers establishing a local RBM process and implementing it in the desired way(29) (135).The concept of RBM implies that the chosen monitoring strategy is adapted to the local and trial-specific context (135). This means that a one-size-fits-all model is not possible (122). The implementation of RBM, with the consequent adjustment or reduction of onsite monitoring visits and source data verification (SDV), can only succeed after establishing an appropriate RBM approach

(10, 128). The way that risks are identified, evaluated and mitigated through clinical trial monitoring requires a change in the mind-set of those who have applied GCP and traditional 100% on-site monitoring since the ICH GCP guidelines were first published in 1996(102, 129). In addition, the lack of a gold standard RBM tool makes it difficult for clinical researchers to decide which RBM tool they should use to direct their RBM plans (208). A US based survey of Clinical Research Organizations published in 2016, found the biggest challenges with implementing RBM are a lack of internal knowledge and expertise to perform RBM along with a perceived inability to maintain enough quality through RBM and lack of capacity to rapidly adapt to changing RBM needs (121). The results of this survey suggest the need for a cultural shift in how many clinical trial teams conduct clinical trial monitoring (24).

With one of the main barriers to RBM implementation being lack of education, clinical trial regulators in the US, Europe and Japan have driven initiatives to educate their clinical researchers and by doing so support the transition of clinical trial monitoring to RBM in their local clinical trial organisations (12, 19, 23, 134). For example, in 2011, the MHRA in the UK developed and published a RBM tool(28). In 2014, Switzerland became the first European country to introduce a regulation adopting risk-based categorization into their clinical trial methodology (135). In contrast, Ireland does not have a national strategy to educate clinical researchers on how they should introduce and implement RBM into their publicly funded, academic run clinical trial units. In 2017, I conducted a national mix-methods study that examined the perceived barriers and facilitators to RBM implementation in academic- led clinical trials in Ireland. The study showed that 14% of participants were not familiar with the term RBM. Almost two thirds of these participants identified lack of education as a very important barrier with almost 20% of participants feeling they did not have the expertise to use a RBM tool (Chapter 4)

The aim of the current study was to develop, implement and evaluate an educational Quality Improvement (QI) intervention to teach academic clinical researchers in Ireland about RBM tools and by doing so change their monitoring behaviour and support them to use RBM tools when developing monitoring plans for their clinical trials. Educational QI intervention provide an opportunity for participants to increase

their knowledge or understanding of a specific topic and by doing so allows the mechanism to drive behaviour change(228, 229).

6.3 Methods

6.3.1 Study Design

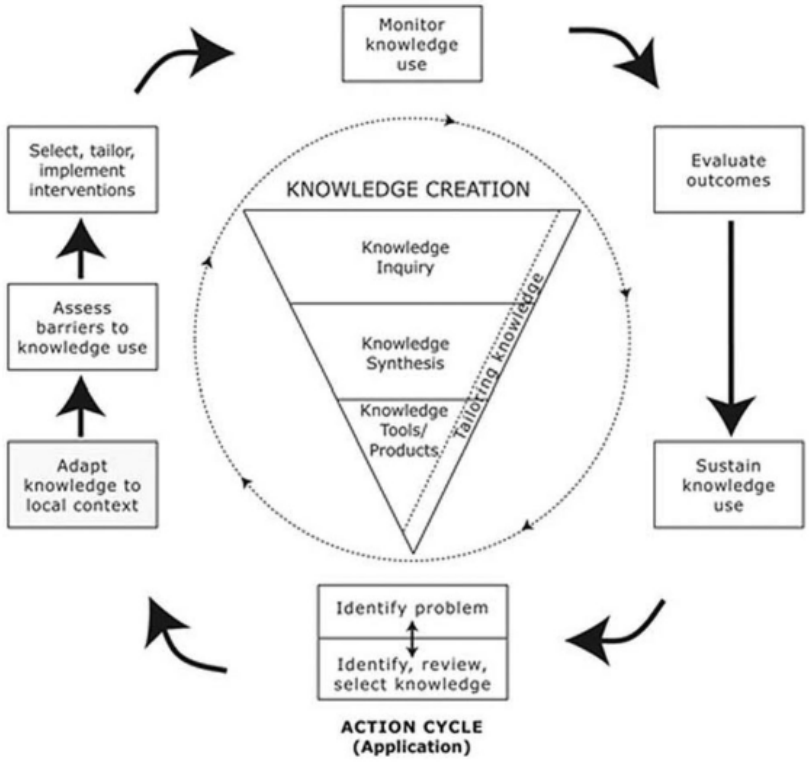
This study was a QI educational intervention conducted in four, publicly funded, academic run clinical trial units in Ireland. QI interventions aim to support change and improve processes by means of an organizational or structural change(147).

6.3.2 QI Intervention –development

6.3.2.1 Conceptual framework

The QI intervention was developed in accordance with the Knowledge to Action Framework (KTA). The KTA framework is a conceptual framework for facilitating the use of research knowledge by several stakeholders, such as practitioners, policymakers, patients, and the public (Figure 9).

Figure 8: Knowledge to Action Framework



The KTA process has two components: (1) knowledge creation and (2) action which have seven phases listed below (151)

1. Identify a problem that needs addressing and select the knowledge or research relevant to the problem (e.g. practice guidelines or research findings)
2. Adapt the identified knowledge or research to the local context
3. Assess barriers to using the knowledge
4. Select, tailor, and implement interventions to promote the use of knowledge (i.e., implement the change)
5. Monitor knowledge use
6. Evaluate the outcomes of using the knowledge
7. Sustain on-going knowledge use

Phase 1- 3 of the KTA framework (problem identification and barriers to knowledge use) were discussed in detail in Chapter 3- *Risk based monitoring (RBM) tools for clinical trials: A systematic review* and Chapter 4- Perceived *barriers and facilitators to Risk Based Monitoring in academic- led clinical trials: a mixed methods study.* The results of Phase 1-3 of the KTA framework informed the development of the QI intervention discussed in this study.

This study will only focus on Phase 4, 5 and 6 of the KTA process which involves the selection, tailoring and implementation of an intervention to promote knowledge use, monitor its use and evaluate the outcomes of using this knowledge.

6.3.2.2 **Intervention development team**

Clinical researchers were the target study population for the QI intervention. In December 2016, I recruited an expert panel of clinical researchers to direct the development of the QI intervention to ensure the intervention would be applicable to the target study group. The expert panel consisted of seven clinical trial experts which included a trial sponsor (1), principle investigators (2), trial coordinator (1),

quality manager (1) and a trial doctor (1) and a clinical trial monitor (1). All panel members had a minimum of three years and maximum of twenty years' experience of developing and implementing clinical trial monitoring plans in Clinical Trials of Investigational Medicinal Products (CTIMPs).

6.3.2.3 QI development process

One researcher (CH) carried out data collection and intervention development. The intervention development was directed by the Consensus-Oriented-Decision-Making (CODM) model. The CODM was used to guide the expert panel to reach a consensus on the RBM tool intervention (33). The CODM model is a decision-making process that includes the following steps:

1. Framing the topic
2. Open discussion
3. Identifying underlying concerns
4. Collaborative proposal building
5. Choosing a direction
6. Synthesizing a final proposal
7. Closure (33).

In March 2017, each member of the expert panel was sent a summary of the findings from Phase 1 -3 and of the KTA Framework as follows: Chapter 3- *'Risk based monitoring (RBM) tools for clinical trials: A systematic review'* The findings from the systematic review found a lack of a gold standard RBM tool as usability of the RBM tools had not been tested. However, in the absence of a gold standard RBM tool, the systematic review identified criteria that clinical researchers RBM too. The criteria are:

1. ensuring the RBM tool assesses risks in accordance with the Risk Indicator Taxonomy for supervision of clinical trials on medicinal products
2. confirming the RBM tool can direct both on-site and centralised monitoring
3. checking the tool provides a process for systematic review of the trial's risk profile

4. ensuring the RBM tool is cost efficient as cost varies significantly between tools

The expert panel were provided with a copy of only three RBM tools that fulfilled the four-selection criteria listed above Risk Assessment Tool (RAT) (22), Risk assessment for risk adapted monitoring (RARAM) (159) and the Risk Assessment Categorisation Tool (RACT) (20) (Table 15). The expert panel were asked to use their experience of conducting clinical trials to provide suggestions on how best to introduce these RBM tools to an academic clinical trial community in Ireland. The expert panel were asked to consider the following points:

- Intervention participants
- Duration of the intervention
- Mode of delivery i.e. online or face to face
- Frequency of the intervention i.e. once off event or multiple sessions
- Intervention assessment - required or not necessary

The expert panel had two weeks to review the findings and to suggest a possible educational intervention (through email, telephone or face to face correspondence) that would support the introduction of RBM tools into academic run clinical trial units in Ireland. At the end of the review period, CH had received feedback from all seven expert panel member. The results were combined using the majority decision rule. This meant that a characteristic of the educational intervention was selected if the majority decision rule of expert members had suggested it.

A brief (two hours maximum in duration), once off educational face-to-face interactive workshop was identified as the most appropriate way to introduce RBM tools into academic led clinical trial units in Ireland.

Table 17: RBM tool characteristics

			Criteria 1	Criteria 2	Criteria 2	Criteria 3	Criteria 4
Author	**RBM tool**	**Mode of administration**	**Risks as mapped to risk indicators taxonomy for supervision of clinical trials of medicinal products**	**Provide recommendation for onsite monitoring**	**Provide recommendation for centralised monitoring**	**Provides recommendations for systematic review of trial's risk profile**	**Cost**
Nordic Monitoring Network (NORM)(27)	Risk Assessment Tool (RAT)	Paper	Yes	Yes	Yes	Yes	Free
Swiss Clinical Trial Organisation (SCTO)(170)	Risk assessment for risk adapted monitoring (RARAM)	Electronic via Microsoft Excel	Yes	Yes	Yes	Yes	Free
TransCelerate BioPharma Inc.(26)	Risk Assessment Categorisation Tool (RACT)	Electronic via Microsoft Excel	Yes	Yes	Yes	Yes	Free

6.3.3 QI Recruitment/ Study participants

The QI intervention was delivered in four academic run clinical trial units in Ireland. Each of the four clinical trial units deliver research across numerous clinical specialties including oncology, cardiology, neurology, ophthalmology and neonatal research in accordance with the EU Clinical Trials Directive and the new ICH GCP guideline(64). At the time of QI study, none of the units used a RBM tool and none had conducted RBM.

Recruitment took place over 4 weeks from the 7th March to the 4th of April 2017. On the 7th of March 2017, I sent an invitation by email to the Quality and Regulatory Affairs Managers in each of the four units. The email included a protocol outlining the aim and outline of the QI intervention (Appendix E). When the Quality and Regulatory Affairs Managers agreed to participate in the QI intervention, they were asked to assemble a Multidisciplinary Testing Team (MDTT). For this study, we defined a MDTT as a collection of members within each clinical trial unit who normally develop, write, review and approve monitoring plans for trials that their clinical trial unit manages. In total, the four MDTTs consisted of 12 participants; study doctor (n=1), quality and regulatory affair managers (n=4), clinical trial monitors (n=5) and research nurses (n=2).

6.3.4 Implementation of the QI intervention

Each MDTT arranged a time and date for their members to participate in the educational workshop between April and June 2017. Each MDTT selected one clinical trial protocol, to which they applied the three RBM tools. The protocol had to pertain to a clinical trial of an Investigational Medicinal Products (IMP) that their clinical trial unit was managing and all members of the MDTT were familiar with. The phase of the clinical trial was not relevant as the three RBM tools can be applied to all clinical trial phases from I-IV(132). The characteristics of the protocols are listed in Table 16.

Table 18: Characteristics of clinical trial protocols

MDTT	IMP trial	Clinical trial phase	Study population	Trial duration	Multi-centre
1	Yes	II	Adults aged≥ 18 years	2 years	Yes
2	Yes	III	Men aged ≥ 18 years	3 years	Yes
3	Yes	III	Adults aged≥ 18 years	2 years	Yes
4	Yes	III	Neonates	3 years	Yes

I facilitated the workshops which all followed the same structure outlined in Table 17. At each workshop, I presented the three RBM tools to the MDTT in the same sequence. First, each MDTT worked through the Risk Assessment Tool (RAT), then through the Risk Assessment for Risk Adapted Monitoring (RARAM) and finally the Risk Assessment Categorization Tool (RACT) (see Table 17). I supported each MDTT to apply the three RBM tools to their selected clinical trial protocol. Throughout the workshop, participants were encouraged to ask questions and discuss the RBM tools. Each workshop lasted approximately two hours.

Table 19: QI intervention schedule

Stage and purpose	Material and rationale for their selection Physical informational materials used in the intervention, including those provided to participants or used in intervention delivery and in training of intervention providers.	Mode of delivery	Allocated time
Stage 1. Introduction To educate participants on the fundamental concepts of RBM to ensure they had enough baseline knowledge required to work the RBM tools	Three paper based RBM guidelines. Guideline used and rationale for its selection are listed below: ▪ **Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (18)** This guideline provides the premise for RBM and explains what clinical trial regulators will expect to see in a RBM plan. ▪ **OECD Recommendation on the Governance of Clinical Trials (10)** This guideline was the first and only document to define and explain the characteristics of a RBM tool. ▪ **Risk indicator taxonomy for supervision of clinical trials on medicinal products (125)** First peer reviewed paper explaining the risk assessment process of involved in RBM and identified and categorized I risk indicators that may	**Flipped classroom session**-flipped learning is a teaching approach in which the conventional notion of classroom-based learning is inverted, so that students are introduced to the learning material before class, with classroom time then being used to deepen understanding through discussion with peers and problem-solving activities facilitated by a teacher. **Implementation** • A week prior to the QI intervention, the facilitator sent the MDTT an electronic copy of the teaching material. Each member of the MDTT and prepare questions to discuss at the start of the QI intervention • At the start of the QI intervention the MDTT together with the facilitator discussed the three RBM guidance and how they applied to their clinical trials. In addition, the facilitator answered questions the MDTT had regarding the development and implementation of the guidance.	15 mins

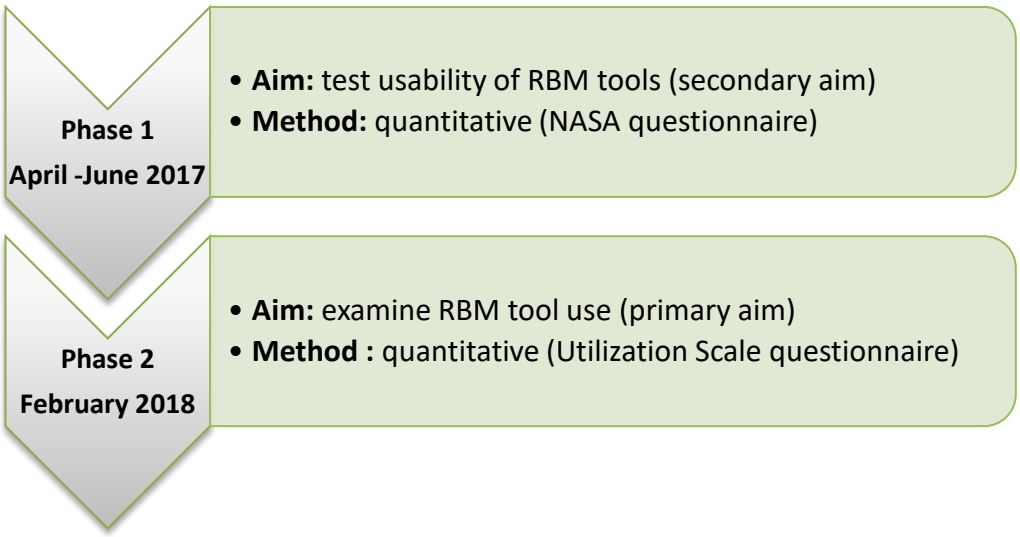
	present an elevated safety and/or ethical risk for participants, and/or for data in a clinical trial.		
Stage 2: Application of the RBM tools The MDTT applied each RBM tool to their chosen protocol. The aim of this was for the facilitator to engage the participants actively in learning how to use the RBM tools. The facilitator supported the MDTTs to actively use the RBM tools	The QI intervention included three paper based RBM tools the Risk Assessment Tool (RAT) (22), Risk assessment for risk adapted monitoring (RARAM) (159) and the Risk Assessment Categorisation Tool (RACT) (20) Each of the three RBM tools included in the QI intervention fulfilled four criteria for a RBM tools. They each assessed risks in accordance with the Risk Indicator Taxonomy for supervision of clinical trials on medicinal products. They supported both on-site and centralised monitoring and provided a process to systematically review trial's risk profile. Finally, each tool was cost efficient as cost as they were freely available on the internet.	**Interactive workshop**	90(30mins for each RBM tool)
Stage 3: Evaluation To evaluate the outcome of the QI intervention – first to assess the usability of the RBM tools and secondly to determine if the intervention supported the participants to change their monitoring behaviour and use RBM in their clinical trials.	▪ **NASA Task Load (NASA-TLX) questionnaire –** is a paper-based questionnaire that measured the measured workload of a task.	**Self-administered face to face –** traditional paper and pencil-based questionnaire After each MDTT applied the three RBM tools to their selected clinical trial protocol, they completed three NASA-TLX questionnaires, each questionnaire measured the perceived workload associated with each RBM tool included in the QI intervention.	15 mins
Stage 4: Follow up To measure how much, if any, the MDTT's had	**Utilization Scale questionnaire** - used to measure how much, if any, the MDTT's had	**Self-administered electronic questionnaire**	Two

used the knowledge they gained in the QI intervention and implemented the RBM tools in their clinical trial units	used the knowledge they gained in the QI intervention and implemented the RBM tools in their clinical trial units. ▪	Six months after participating in the QI intervention, the four Quality and Regulatory Affair Managers from each MDTT, one from each clinical trial unit, were asked to complete a Utilization Scale questionnaire The Quality and Regulatory Affair Managers were the only members of each MDTT asked to complete this questionnaire because they coordinate clinical trial monitoring in their clinical trial unit.	weeks to complete

6.3.5 Data collection and analysis

Separate data were used to first examine the usability of the RBM tools and then to examine if the use of RBM tools had increased among the study population after participating in the QI intervention. This occurred in two phases as described in detail below and summarised in Figure 8.

Figure 9: Data collection and analysis



6.3.5.1 Phase 1: test usability of RBM tools

The usability of the RBM tools was assessed using the NASA Task Load (NASA-TLX) questionnaire(230, 231). This is a widely used, subjective, multidimensional assessment tool that rates perceived workload in order to assess a task, system, or team's effectiveness or other aspects of performance(231). Originally developed as a questionnaire to measure mental workload, the NASA TLX questionnaire has been adopted to measure usability(232). It was developed by the Human Performance Group at NASA's Ames Research Center in the 1980s, over a three year validated cycle. It has been cited in over 4,400 studies, in a variety of domains, including aviation, healthcare and other complex socio-technical domains(231).

The NASA TLX questionnaire measures the total workload of a task by dividing it into six subjective subscales, measured on a 21-point Likert scale (Appendix E). The subscales are:

- **Mental Demand -** how much mental and perceptual activity was required? Was the task easy or demanding, simple or complex?
- **Physical Demand -** how much physical activity was required? Was the task easy or demanding, slack or strenuous?
- **Temporal Demand -** how much time pressure did you feel due to the pace at which the tasks or task elements occurred? Was the pace slow or rapid?
- **Overall Performance -** how successful were you in performing the task? How satisfied were you with your performance?
- **Frustration Level-** how irritated, stressed, and annoyed versus content, relaxed, and complacent did you feel during the task?
- **Effort-** how hard did you have to work (mentally and physically) to accomplish your level of performance?

NASA TLX questionnaire Analysis

Each member of the MDTT completed a NASA TLX questionnaire after they used each RBM tool. The completed NASA TLX questionnaires were analysed in SPSS version 11 using the Raw Task Load Index (RTLX) which is a validated scoring system that calculates the individual and combined perceived workload of each of the six subscales as either low, medium or high(233). If a subscale receives a score of ≤7 it is categorised as having a low perceived workload; if it receives a scores >7 and ≤14 it is categorised as having a medium perceived workload and if a subscale dimension is scored between >14 and ≤21 it is categorised as having a high perceived workload. The overall workability score for each RBM tool is the average of the combined workability subscale score(233).

6.3.5.2 Phase 2: examine RBM tool use

The Utilization Scale was used to measure how much, if any, the MDTT had implemented the RBM tools in their clinical trial units. The Utilization Scale is a validated questionnaire developed by Larsen in 1982. It accesses seven ranked stages of knowledge use and non-use(234). The seven stages of knowledge utilisation are:

- **Nothing done:** No action, not even discussion, happened
- **Considered and rejected:** Some discussion took place, but the RBM tool was rejected
- **Under consideration**: RBM tool has not been used but is being discussed and considered.
- **Steps toward implementation:** Although the RBM tool has not yet been used, the decision to do so has been made and initial planning steps have been taken.
- **Partially implemented:** Certain features of the RBM tool have been used, whereas others have been disregarded.
- **Implemented as presented:** The RBM tool was used in the form in which it was originally presented.
- **Implemented and adapted:** The RBM tool was modified or adapted to fit our local situation

Utilization Scale – data collection

Six months after participating in the QI intervention, the four Quality and Regulatory Affair Managers from each MDTT, one from each clinical trial unit, were asked to complete a Utilization Scale questionnaire (Appendix E). The Quality and Regulatory Affair Managers were the only members of each MDTT asked to complete this questionnaire because they coordinate clinical trial monitoring in their clinical trial unit.

6.3.6 Ethical Approval

Under the Irish Health Service Executive, quality assurance studies and service evaluation studies do not require Research Ethics Committee (REC) approval(235). They define such studies as having the following characteristics:

- they are designed to produce information to inform delivery of best practice.
- they involve an intervention that is not randomly allocated but is selected by healthcare professionals.
- they include the administration of simple interviews and questionnaire(235).

Our QI intervention met these criteria and so REC approval was not required. However, to ensure participant's safety and integrity, the QI intervention was conducted in accordance with research ethic procedures. Before each educational workshop commenced, I explained the aim and purpose of the QI intervention to each member of the MDTT. In addition, I informed participants that they could withdraw from the study at any time during the workshop or follow up. All participants gave verbal consent to participate in the workshop. All participant data were anonymized and stored securely.

6.4 Results

6.4.1 NASA TLX questionnaire

The NASA TLX questionnaire results are presented for each of the six subscales of workability and then a combined score for each RBM tool was calculated for each RBM tool.

6.4.1.1 Workability dimension – MDTT scores

The results of the NASA TLX questionnaire show that the Risk Assessment Tool (RAT) was the only RBM tool to receive a low mental demand score (Table 20). The four MDTTs gave each RBM tool a low score for physical demand. The Risk Assessment Categorisation Tool (RACT) was the only RBM tool to receive a high score for temporal demand. The RAT and the Risk assessment for risk adapted monitoring (RARAM) were the only tools to receive a low score for frustration level by MDTT 3 and 4.

6.4.1.2 Workability dimension per RBM tool

All RBM tools scored an overall medium workability score besides the RAT which received a low overall workability score from MDTT 3 (Table 20).

Table 20: NASA TLX questionnaire results for each MDTT

***Score Rating:** **Low** = score of ≤7; **Medium**= >7 and ≤14**;** **High**= >14 and ≤21

RBM tool	Mental	Physical	Temporal	Performance	Frustration	Effort	Overall score	Average score
MDTT 1								
Risk Assessment Tool (RAT)	10	2	5	8	19	16	60	10 **Medium**
Risk assessment for risk adapted monitoring (RARAM)	16	1	3	15	18	2	55	9 **Medium**
Risk Assessment Categorisation Tool (RACT)	14	1	4	3	17	17	54	9 **Medium**
MDTT 2								
Risk Assessment Tool (RAT)	4	1	4	17	16	4	47	8 **Medium**
Risk assessment for risk adapted monitoring (RARAM)	10	1	6	13	18	21	69	12 **Medium**
Risk Assessment Categorisation Tool (RACT)	16	1	13	3	21	12	67	11 **Medium**
MDTT 3								
Risk Assessment Tool (RAT)	5	1	4	8	3	4	25	4 **Low**
Risk assessment for risk adapted monitoring (RARAM)	19	1	11	6	20	19	78	13 **Medium**
Risk Assessment Categorisation Tool (RACT)	15	1	18	9	18	13	74	12 **Medium**
MDTT 4								
Risk Assessment Tool (RAT)	5	1	8	15	5	6	40	7 **Medium**

Risk assessment for risk adapted monitoring (RARAM)	16	1	10	9	3	11	50	8 **Medium**
Risk Assessment Categorisation Tool (RACT)	17	2	19	3	18	18	77	12 **Medium**

6.4.2 Utilisation Scale

Table 21 outlines the results of the Utilisation Scale questionnaire. Results show that three MDTTs have taken steps or have fully implemented a RBM tool into their clinical trial unit. MDTT 1 has taken steps to introduce the Risk assessment for risk adapted monitoring (RARAM) into their clinical trial unit. MDTT 3 also adapted the RAT to the needs of their clinical trial unit and has implemented the modified version. MDTT 4 has implemented the Risk assessment for risk adapted monitoring (RARAM) as presented. MDTT 2 was the only clinical trial unit not to implement one of the RBM tools into their clinical trial unit.

The Risk assessment for risk adapted monitoring tool (RARAM) had the greatest level of uptake as two of the MDTTS have taken steps to introduce this tool into their clinical trial unit. The Risk Assessment Tool (RAT) was the only tool to be adapted and implemented into a clinical trial unit. Finally, the Risk Assessment Categorisation Tool (RACT) was the only tool not to be implemented into a clinical trial unit.

Table 21: Utilisation Scale

***Score Rating:** **Low** = score of ≤7; **Medium**= >7 and ≤14**;** **High**= >14 and ≤21

RBM tool	RBM tool was considered but rejected	RBM tool was not considered or even discussed	RBM tool in under consideration	Steps have been taken towards implementing the RBM tool	RBM tool was implemented as presented	RBM tool was adapted to the clinical trial unit's need and then implemented
RAT[1]	**Yes**	No	No	No	No	No
RARAM[2]	No	No	No	**Yes**	No	No
RACT[3]	No	**Yes**	No	No	No	N0
MDTT 2						
RAT[1]	**Yes**	No	No	No	No	No
RARAM[2]	**Yes**	No	No	No	No	No
RACT[3]	No	**Yes**	No	No	No	No
MDTT 3						
RAT[1]	No	No	No	No	No	**Yes**
RARAM[2]	No	**Yes**	No	No	No	No
RACT[3]	**Yes**	No	No	No	No	No
MDTT 4						
RAT[1]	**Yes**	No	No	No	No	No
RARAM[2]	No	No	No	No	**Yes**	No
RACT[3]	**Yes**	No	No	No	No	No

[1] RAT = Risk Assessment Tool
[2] RARAM = Risk assessment for risk adapted monitoring
[3] RACT = Risk Assessment Categorisation Tool

6.5. Discussion

RBM is now the recommended method of clinical trial monitoring(23). However, at present, many clinical researchers are not sufficiently ready, trained, or experienced to perform RBM (30, 135, 219). In addition, there is evidence that suggests clinical researchers do not have confidence in their ability to adapt and apply RBM in their organisations(219). As far as we are aware, the study reported in this chapter is the first Quality Improvement (QI) intervention to support the introduction of RBM into academic led clinical trial units. To date, QI interventions have led to changes that have produced better patient outcomes, better system performance and better professional development(147). However, there is a paucity of evidence documenting the value of QI to promote high quality and efficient clinical trials(148). Our study supports the global initiative aimed at increasing QI use in clinical trials to improve clinical trial methodology (148-150)

Presently, RBM tools provide the most comprehensive and structured guidance for RBM implementation(10, 132). Our educational workshop included three RBM tools that met four pre-defined RBM tool selection criteria(132). Accordingly, all three RBM tools assess clinical trial risks that are set out in the Risk Indicator Taxonomy for supervision of clinical trials on medicinal products; they direct both on-site and centralized monitoring; they provide a process to systematically review a trial's risk profile and are all freely available online(132).

This study used the Utilization Scale questionnaire to assess if and how the MDTTs implemented one or more of the RBM tools into their clinical trial unit. The MDTTs completed the Utilization Scale questionnaire eight months after the new ICH GCP guideline came into effect; and a minimum of six months after they participated in the QI intervention. The follow up period was sufficient to allow for an accurate assessment of the workshop's impact (236). The results of the Utilization Scale questionnaire show that three of the four MDTTs have taken steps to implement at least one of the RBM tools into their clinical trial unit. With two MDTTs adapting an RBM tool to the need of their clinical trial unit and implementing the revised version. However, if was not possible to identify how or why the RBM tools were adapted as

the Utilization Scale questionnaire did not include open ended questions exploring this decision. Only one of the MDTTs (MDTT 2) either considered and rejected or did not consider implementing one of the three RBM tools into their clinical trial unit.

Since three of the four MDTTs implemented one of the RBM tools into their clinical trial unit, our findings suggest that the QI intervention was somewhat effective in supporting the use of RBM tools in academic-run clinical trial units in Ireland. However, this conclusion should be considered with caution. QI interventions lack many of the stable characteristics generally assumed for studies of effectiveness(237, 238). For example, like many other QI interventions, this study did not have a control group and participants were purposely (rather than randomly) sampled(237). The differing characteristics of the study participants, the RBM tools and the organizations where the interventions were implemented, also makes it difficult to predict the effectiveness of a similar QI intervention or whether the effectiveness of our QI intervention would be similar in other settings(237). Furthermore, this QI study used an educational intervention based on three RBM tools. Conclusions from studies of educational interventions cannot be taken in isolation, but also need consideration of the characteristics of the knowledge that was being transferred, the teacher/facilitator, and participating individuals and organizations(238, 239). For instance, a different facilitator, different participants or different RBM tools in a similar QI study may have a different effect on the uptake of RBM tools(238, 240).

Overall there is a need for future studies to evaluate the implementation of the RBM tool -QI intervention. Such an implementation evaluation would identify which elements were implemented as planned and which were not, discern the intervention's strengths and weaknesses, and study its internal validity by assessing the cause and effect relationship. For example the three RBM tools were also presented to each MDTT in the same sequence. First, each MDTT worked through the Risk Assessment Tool (RAT), then through the Risk Assessment for Risk Adapted Monitoring (RARAM) and finally the Risk Assessment Categorization Tool (RACT) .This delivery of the RBM tools may have introduced a learning effect into the study, where the first RBM tool used by each MDTT may have impacted on their understanding of the second and three RBM tool their used(241, 242). Therefore the usability of each

RBM tool may have shrewd by the sequence in which they were presented during the QI intervention.

Finally, we developed this study in February 2017, five months before the new ICH-GCP came in effect in June of that year(23). Our QI intervention included the three RBM tools that employ a standardised, fixed risk assessment process(243). This means that these tool assess clinical trial risks using pre-defined risk indicators that cannot be modified to for each clinical trial; such risks relate to the study population or the investigational medicinal product, (132, 243). For example, these tools provide the same standard risk assessment process for a Phase II neonatal trial and a Phase III adult trial(27, 170). Since the implementation of our QI intervention, there has been significant increase in studies describing and evaluating RBM tools and RBM (113, 244). Recently published literature, would suggest that a generic risk assessment process may not be appropriate for RBM tools as they don't accommodate the unique risk profile of each clinical trial.(244) Studies now suggest that RBM tools should use a dynamic risk assessment process that enables clinical researchers to respond to changing clinical trial circumstances (113, 244). Such frameworks allow clinical researchers to use their historical experience of managing clinical trials in certain disease areas, to develop a data driven risk assessment that includes specific risks that pose a potential risk to the integrity of data collected in their trial. Then clinical researchers should develop their own suite of operational procedures they can employ to mitigate risks as they emerge throughout the lifecycle of a trial(244). Clinical trial units in Ireland should use this dynamic risk assessment approach to develop a RBM tool that meets the needs of their organisation.

To date, evidence supporting the effectiveness of RBM tools in developing an effective monitoring plan is lacking (132). This is to be expected, as RBM tools are merely an instrument to guide RBM(10). Therefore, their effectiveness will be affected by clinical trial variables that are difficult, if not impossible, to control such as the experience of the clinical trial team, the IMP, clinical trial budget and the unpredictable risks of the study population(26). However, usability provides a marker for RBM tool quality as it assesses the extent to which an RBM tool can be used by clinical researchers to achieve RBM goals with effectiveness, efficiency, and

satisfaction(245). In essence, a RBM tool designed for use by clinical researchers, should be easy to use, easy to learn, easy to remember (the instructions), and helpful to users(246).

The NASA TLX questionnaire measured usability using six dimensions of workability which include mental demand, physical demand, temporal demand, overall performance, frustration level and effort(231). The results of the NASA TLX questionnaire show that none of the three RBM tools received low scores for all six dimensions of workability. All three RBM tools received an overall medium score for usability. However, usability is a complex topic and therefore the quantitative survey used in this study, by itself does not provide an in depth analysis of the usability of RBM tools (247-249). More research is needed to fully understand if characteristics of a RBM tool impact on their usability (247-249). For instance, it would be helpful to conduct a qualitative study to explore the results of the NASA TLX questionnaire. Such a study would explore why the participants graded certain workability dimensions as low, medium or high. This information could be used to develop barriers and facilitators associated with RBM tool use (219).

Given the limitations of our study, the generalizability of its findings should be interpreted with a degree of caution. However, by disseminating our experiences, we are supporting an ancillary recommendation by the Clinical Trials Transformation Initiative (CTTI) project on effective and efficient monitoring, to “share knowledge and experiences, so that best practices may be established”(29).

Conclusion

This is the first quality improvement (QI) intervention to support the introduction of RBM tools into academic led clinical trials units. Our findings show that a brief, face-to-face, interactive, educational workshop improves the use of RBM tools in clinical trials. This study supports the global initiative aimed at increasing QI use in clinical trials as one means to improve clinical trial methodology (148-150).

Chapter 7. Discussion

7.1 Introduction

The overarching aim of this thesis was to develop, implement and evaluate a quality improvement intervention to support the introduction of Risk Based Monitoring (RBM) into academic-led clinical trials in Ireland. This research started in 2014, in anticipation of the revised ICH-GCP guidelines, which came into effect on 14 June 2017, which brought RBM to the forefront of clinical trial monitoring(126).

This chapter firstly outlines the main findings of this thesis. Secondly, the main strengths and limitations of this work are highlighted. Thirdly, implications for practice are outlined. Fourthly, areas of future research are proposed. Finally, I provide a brief conclusion to the thesis.

7.2 Summary of findings

This thesis included four individual pieces of research that were guided by the components of the KTA framework (Table 22). The specific objectives of each piece of research were informed by the core components of the KTA framework, which are knowledge creation and the application of this knowledge into practice(151). This meant that at least one of the research elements had to create RBM knowledge, as knowledge creation is a core component of the KTA framework. Below is a summary of the key findings from each phase of the research(151)

.

Table 22: Application of the KTA framework

Phase	KTA component	Objective	Study design	Key findings
1	**Knowledge creation**	Examine how should RBM be implemented	Systematic review	Ninety-one potential RBM tools were identified and 24 were eligible for inclusion. These tools were published between 2000 and 2015. Eight tools were paper based or electronic questionnaires and 16 operated as Service as a System (SaaS). Risk associated with the investigational medicinal product (IMP), phase of the clinical trial and study population were examined by all tools and suitable mitigation guidance through on-site and centralised monitoring was provided. It was possible to identify "best" RBM technique or tool as none of the RBM tools had been evaluated.
2	**Action Cycle** • Identify problems and select knowledge • Adapt knowledge to local context • Assess barriers to knowledge use	Identify the barriers and facilitator to RBM implementation in academic-led clinical trials in Ireland?	Mixed methods-quantitative & qualitative study	Barriers to RBM implementation included lack of RBM knowledge/training, increased costs caused by greater IT demands, increased workload for trial staff and lack of evidence to support RBM as an effective monitoring approach. Facilitators included participants' legal obligation to perform RBM under the new ICH-GCP guideline, availability of RBM guidance and perception of cost savings by performing RBM in future trials.

3	**Knowledge creation**	Investigate the difference between on-site and centralised monitoring in the TRUST study.	Document analysis	We found that on-site monitoring was used more frequently than centralised monitoring in the TRUST study. Sixteen of the seventeen recommended GCP monitoring activities were completed through on-site visits. In contrast, only eleven of the seventeen recommended monitoring activities were completed through centralised monitoring.
4	**Action cycle** • Select, tailor and implement intervention • Monitor knowledge use • Evaluate outcome • Sustain on-going knowledge use	Identify a suitable KT strategy to support the introduction and on-going use of RBM in academic-led clinical trials in Ireland	Mixed methods	The findings of the study show that a brief, face to face, interactive education workshop is an effective way to encourage RBM tool usage in academic led clinical trial units in Ireland.

7.2.1 Phase 1: Knowledge creation

Phase one of the thesis (chapter 3) involved the creation of RBM knowledge through the completion of a systematic review of RBM tools. The study was published in *Contemporary Clinical Trials* in 2016*(132)* and, as of September 2018, has been cited in six peer-reviewed papers and downloaded almost two thousand times, and the findings have been presented at two international and three local conferences.

The review identified 24 RBM tools that met the Organisation for Economic Co-operation and Development (OECD) classification of RBM tools(132). These tools were published between 2000 and 2015. Eight tools were paper-based or electronic questionnaires and 16 operated as Service as a System (SaaS). All tools examined risks associated with the investigational medicinal product (IMP), phase of the clinical trial and study population and provided suitable mitigation guidance through on-site and centralised monitoring.

However, the review did not identify a gold standard RBM technique or tool because none of the tools had been validated (3). It concluded that the lack of a validated approach used by RBM tools would make it difficult for clinical researchers to decide which RBM tool they should use when developing their RBM plan (3). To overcome this challenge, I applied the findings of the review to the ICH GCP's and the OCED's guideline for RBM and developed four criteria that should be considered when choosing a RBM tool (4, 6). These are:

1. Ensure the RBM tool's baseline risk assessment process examines the risk indicators set out in the Risk indicator taxonomy for supervision of clinical trials on medicinal products.
2. Ensure the RBM tool can support both on-site and centralised monitoring. For SaaS tools ensure that on-site monitoring data can be entered manually into the electronic data capture system.
3. Ensure the RBM tool provides a process for systematic review of the trial's risk profile.

4. Ensure the RBM tool is cost efficient i.e. the paper-based tools are available free of charge however they need the support of an EDC system to perform centralised monitoring.

The creation of criteria for RBM tool selection, along with the identification of 24 RBM tools were the main findings to arise from the systematic review.

7.2.3 Phase 2- Action cycle

Phase two of my thesis (chapter 4) was based on the action cycle of the KTA (Table 22). The aim of this phase was to complete the first, three subcomponents of the action cycle; which are to identify problems and select knowledge, adapt knowledge to local context and access barriers to knowledge use. To fulfill these criteria, I conducted a mixed methods study, which was published in *Trials* in 2016 (219) and was accepted for oral presentation at the Society for Clinical Trials 39th Annual Meeting in Portland, 2018.

The results of the study showed that participant's inexperience of using RBM tools and performing centralised monitoring were the main barriers to RBM implementation(219). Most participants in this mixed methods study had never used or even knew what a RBM tool was. The study concluded that to increase the use of RBM tools, Irish clinical trial regulators should develop or select an approved RBM tool at a national level(219).

Overall, this study confirmed the absence of, and the need for, training and the availability of guidelines to support the implementation of RBM in academic-led clinical trials through an increased use of RBM tools and centralised monitoring.

7.2.3 Phase 3 – Knowledge creation

The results of Phase 2 (chapter 4), mixed methods study showed that academic clinical researchers in Ireland had limited experience of conducting centralised monitoring and felt ill equipped to perform this monitoring method compared to on-site monitoring(219). This result reflected the lack of centralised monitoring guidelines that existed(20). At that time point in my research for this thesis, only two studies had

retrospectively compared monitoring practices by testing if on-site monitoring findings could have been identified through centralised monitoring(20). Findings, from those two studies suggested critical on-site monitoring findings such as incorrect participant consent processes and inappropriate IMP dispensing could have been identified through central monitoring techniques. However, the results of those studies are limited: both used arbitrary criteria to classify monitoring activity and neither reviewed all monitoring findings from a completed trial (127, 226).

To overcome this evidence gap, I conducted a Study Within a Trial (SWAT) to provide the first document analysis of on-site and centralised monitoring reports collected prospectively in a recent international multi-centre clinical trial - The TRUST Thyroid Trial(221). This study is called "On-site versus centralised monitoring – the TRUST Thyroid Trial experience' and described in detail in Chapter 5.

The SWAT used deductive qualitative document analysis approach to compare both monitoring approaches by examining their use to fulfil ICH GCP's monitoring guidance. Initially, I believed the results of this study would support the development of RBM guidelines. However, the external validity of the study results was limited because they were generated from a document analysis of a single clinical trial.

7.2.4 Phase 4 – Action cycle

The aim of Phase 4 (chapter 6) of the thesis was to complete the last four subcomponents of the Action cycle; which are select, tailor and implement a KT intervention, monitor its use, evaluate its outcome and sustain on-going knowledge use(151). To fulfill these criteria, I conducted a quality improvement (QI) study titled '*Introducing Risk-Based Monitoring tools into academic-led clinical trial units in Ireland: a quality improvement intervention'.*

The aim of this QI study was to determine if a brief, educational, interactive, face-to-face workshop would result in increased use of RBM tools by academic clinical researchers in Ireland. Additionally, the study tested if RBM tool usability was linked to its usage. The results of the study show that a brief, face-to-face, interactive education workshop is an effective way to encourage RBM tool usage. This study

supports the global initiative aimed at increasing QI use in clinical trials to improve clinical trial methodology(237). However, this result should be considered with caution. QI interventions lack many of the stable characteristics generally assumed for studies of effectiveness(237). For example, like many other QI interventions this study was not controlled, participants were purposely and not randomly sampled (147, 237). Due to differing characteristics of the study participants, the RBM tools and the organizations where the interventions were implemented, it is difficult to predict the effectiveness of a similar QI intervention or suggest its effectiveness would remain constant in differing contexts(237).

7.2.5 Overall findings

The findings of the thesis show that applying the KTA framework to empirical data guided by stakeholder engagement can led to an intervention that is implementable in clinical practice and has the potential to positively change clinical researchers monitoring practices. This thesis provides critical evidence on the complexities associated with implementing RBM in academic-led clinical trials. It provides practical recommendations to guide clinical researchers who wish to perform RBM.

7.3 Strengths and weaknesses

Strengths

This section provides a synopsis of the overall strengths and limitations of this thesis. The strengths and limitations of the individual papers have been provided in detail in the relevant chapters.

This thesis has addressed a timely and relevant global research question in the area of clinical trial methodology(26). Although the FDA guidance, 'A Risk-Based Approach', has been final for six years, clinical researchers around the world are still struggling to implement monitoring practices that align with RBM(12). My research findings, presented in this thesis, include practical recommendations to guide policy makers, regulators and clinical researchers in developing strategies to support the implementation of RBM in their clinical trials units. The relevance of the findings to researchers organising clinical trials is shown by the fact that this work has been

presented at several scientific conferences both nationally and internationally (Appendix G and H). Furthermore, two of the four original research papers have already been published in peer-reviewed scientific journals (Appendix H). For this thesis, at the end of this series of studies, the main product is a carefully developed Quality Improvement intervention to support the implementation of RBM.

The systematic review and mixed methods study were conducted to inform the development of a specific intervention. However, the publication of these studies in international journals means they will also inform and benefit the work of other research groups aiming to follow the ICH-CGP guidelines and introduce RBM in their clinical trial units. The systematic review, through the identification and evaluation of grey and peer reviewed RBM tools has provided information on available RBM methodologies(132). It is the first review to systematically identify and compare academic and commercial RBM tools for clinical trial monitoring. It makes a major contribution to the literature on RBM and provides RBM guidance to the global clinical trial community(132). Our findings support the OECD's goal of ensuring appropriate and harmonised understanding of risk assessment (13).

The mixed methods study provides new insight into the barriers and facilitators that encourage or prevent clinical researchers from performing RBM in their clinical trials(219). It is the first comprehensive analysis of clinical trialists' readiness and aptitude for RBM and will provide guidance to the international clinical trial community who strive to implement RBM.

A major strength of the thesis was the inclusion of expertise from cross-functional areas of a clinical trial team(29). Any clinical trial is the result of the efforts of a diverse team including clinicians, monitors, statisticians, trial and data managers, study nurses and data managers(29, 170, 250). RBM, as emphasised throughout the TransCelerate position paper, is a cross-functional process that requires the skills and knowledge of all members of a clinical trial team(26). Similarity Risk ADApted MONitoring (ADAMON) study team call for the perspectives of stakeholders involved in RBM (e.g. trial project leaders or principal investigators) to be considered in the development of future RBM strategies(29). In this thesis, the mixed methods study and Quality

Improvement study included a sample of all the types of researcher who would typically work on a clinical trial in an academic setting. These include PIs, nurses, doctors, monitors, pharmacists, managers and biostatisticians(23). The diverse study population allowed for the collection of data from all types of clinical trial staff.

Thus, an effective RBM plan must utilize the strengths of a clinical trial team(29). Every member of a clinical trial team has a role to play in ensuring that the trial is robust and contributes their personal skills to defining thresholds for unacceptable risk, identifying problematic data, investigating underperforming sites or applying appropriate interventions to minimize or prevent further issues(29). It is likely that no individual team member will be involved in every aspect of RBM, but they should have a good understanding of the importance of their role to ensuring the success of the overall process(170).

In 2012, the OCED in their 'Recommendation on the Governance of Clinical Trials' said that efficient instruction and global training will be a crucial success factor to ensure appropriate and harmonised understanding and use of RBM tools(10). As far as I am aware, this thesis is the first research study to develop, implement and evaluate an educational workshop to support the use of RBM tools. The Quality Improvement study will help the global clinical trial community who wish to follow OECD's recommendations and develop training to support RBM tool use(10, 32).

Finally the thesis was directed by the Knowledge to Action Framework (KTA) (151). This framework has been used in practice with varying degrees of completeness(151). This thesis is one of the few studies that has completed all seven components of the KTA process that include identifying research problems and selecting knowledge ; adapting knowledge to local context; accessing barriers to knowledge use; selecting, tailoring and implementing intervention; monitoring knowledge use and evaluating outcome and sustaining knowledge use.(151). This thesis can be used a guide for other health professionals across the globe who face challenges of translating the best available evidence into timely health interventions that provide the most effective care and service(154).

- **Limitations**

The thesis also had several limitations, and it should be noted that much of the research was conducted before the new ICH-GCP guidelines come into effect on 14 June 2017. A future longitudinal study would allow researchers to track the new ICH-GCP's effect on RBM uptake over time and explore its impact on clinical trial conduct and monitoring outcomes. Such a study could use the mixed methods study results as baseline data.

In addition, as noted above, the results of the brief educational intervention outlined in chapter 4, should be considered with caution. Mainly due to the fact that conclusions about educational interventions cannot be taken on their own without considering the characteristics of the knowledge that was being transferred, the teacher/facilitator, participants and organizations(239). For instance, a different facilitator or different RBM tools in a similar QI study may increase or reduce the uptake of RBM tools(251).

7.4 Implications for Practice

Risk assessment and risk management are two key aspects of RBM implementation (26, 244). RBM is about taking a holistic approach to assess all possible risks related to a clinical trial and then developing an appropriate risk management plan which includes systematic monitoring and controlling/mitigating risks throughout the conduct of a study(23, 244). The correct identification and assessment of study specific risks, categorization and implementation of risk-based study specific monitoring plans are critical components the generation of ensure high quality clinical trial data that will enhance participant protection, build trial efficiencies and optimise clinical trial budgets(110).

Presently, RBM tools provide the most comprehensive and structured guidance for RBM implementation(10, 132). Our educational workshop included three RBM tools that met four pre-defined RBM tool selection criteria(132). Accordingly, all three RBM tools assess clinical trial risks that are set out in the Risk Indicator Taxonomy for supervision of clinical trials on medicinal products; they direct both confirming on-site

and centralized monitoring; they provide a process to systematically review a trial's risk profile and finally they were all freely available online(132).

To date, evidence supporting the effectiveness of RBM tools is lacking(132). This is to be expected, as RBM tools are merely an instrument to guide RBM(10). Therefore, their effectiveness will be affected by uncontrollable clinical trial variables such as the experience of the clinical trial team, the IMP, clinical trial budget and the unpredictable risks of the study population(26). As highlighted in the QI study, clinical researchers have different needs and preferences for RBM tools that they choose to use in their clinical trials units.

In the future, clinical researchers who wish to follow the ICH GCP guidelines and perform RBM should first either select or develop an RBM tool for their clinical trial unit(10, 32). Such a tool should fulfil the OCED's requirement for an RBM tool. Accordingly, firstly they must support the assessment of risk in a clinical trial protocol and secondly, they should provide guidance for subsequent monitoring activity that can mitigate the risk identified (13). It is also important that the usability of an RBM tool is considered before it is selected for use in a clinical trial unit. If an RBM tool has good usability it can be used by clinical researchers to conduct RBM with effectiveness, efficiency and satisfaction.

Furthermore researchers require training on how to use RBM tools(10).Therefore clinical trial units must select the RBM tools that are appropriate for them or develop a bespoke one (10, 32). However, whatever RBM technique is ultimately used, an emphasis on risk-based approaches will force the sponsor to take a more proactive approach to quality through a well-defined protocol, sufficient training and communication by highlighting those data most important to patient safety and the integrity of the final study results. Furthermore, RBM provides an opportunity for clinical researchers to identify the problems early provides the opportunity to refine procedures and address shortcomings as the trial is ongoing(213).

While it may be possible to apply the experience gained in RBM from one trial towards another, it may not be as straightforward as applying the same sets of rules and programs to a new set of data(244). In many instances what constitutes as high risk

depends on several factors related to the disease, sponsor and site experience and the characteristics of the clinical trial(133). First-in-human studies, or trials involving special patient populations (e.g. paediatrics) or severe disease may have a low tolerance for risk among the safety indicators(146, 170). By contrast trials with one or more adaptations, many inexperienced sites or new or unfamiliar equipment may have stricter thresholds for quality metrics. Therefore, clinical trial units must select a RBM methodology that is appropriate for their organisation.

7.4.1 Implications for future RBM practice in clinical trial units in Ireland

The concept of RBM implies that the chosen monitoring strategy is adapted to the local and trial-specific context (127). This means that a one-size-fits-all model is not possible and despite the availability of RBM guidelines, challenges still exist with respect to clinical researchers establishing a local RBM process and implementing it in the desired way (24, 127). Generic RBM tool such as the TransCelerate or the Risk assessment for risk adapted monitoring (RARAM) discussed in Chapter 6, may not be suitable for all clinical trials units.

For clinical trial units that want to implement RBM in their clinical trial units, I recommend that these centers should first develop a RBM tool that is tailored to the needs of their clinical trial network and study population. As defined by the OCED and discussed in detail in Chapter 3, a RBM tool should fulfil two functions, first they must support the assessment of risk in a clinical trial protocol and secondly, they should provide guidance for subsequent monitoring activity that can mitigate the risk identified (10). When developing a RBM tool, clinical trial units should follow the six steps listed below.

1. Assembled a Multi-Disciplinary Development Team

The Multi-Disciplinary Development Team will develop the RBM tool. This team should include membership from each functional area in the clinical trial unit such as the study monitors, in-house clinical research nurses and PIs, biostatistics, clinical trial pharmacists and data management. The team should preferable include patient representatives as they play an important role in trial conduct.

2. Develop a risk assessment process

The Multi-Disciplinary Development Team should then develop a risk assessment process. To be effective and sustainable, the risk assessment process needs to be simple, practical First the team should compile an exhaustive list of risks that they believe are associated with their trials. The Multi-Disciplinary Development Team should conduct this process through facilitated workshop to prevent siloed thinking. Workshops have shown to improve understanding of a risk by bringing together diverse perspectives. For example, when considering a clinical trial risk such as enrolment of an ineligible participants, workshop participants from Principles Investigators, study nurses, data managers, participants and monitors may each bring different information regarding causes, consequences, likelihoods. These risks should focus on patient safety, data quality and study integrity risks. The risks can be identified though a review of the historical experience of the Multi-Disciplinary Development Team's management of clinical trials with a conventional monitoring strategy during the preceding years. Along with analysis of known risks associated with the population and study procedures/drugs.

Once the risks have been identified they must be ranked and prioritised. The risk should be ranked as low, medium or high based on their predicated severity and probability of occurring. The ranking system should be decided by the Multi-Disciplinary Development Team.

3. Develop a risk mitigation / clinical trial monitoring strategy

Instructions enable key players to make sure that the clinical trial is conducted, recorded and reported in accordance with the protocol, standard operating procedures, Good Clinical Practice (GCP) and applicable regulatory requirements. The monitoring plan should define what activities will be conducted off-site and centralized, as well as those that must be performed.

4. Construct a RBM Tool template

Transfer the data risk assessment process and the risk mitigation into one document titled 'Risk Based Monitoring Tool'. Note the Risk Based Monitoring Tool' may need to be tailored for each clinical trial.

5 Test for Usability by internal and external stakeholders

Once the 'Risk Based Monitoring Tool' has been developed, the Multi-Disciplinary Testing team should test its usability with internal and external stakeholders that conduct clinical trials in the clinical trial unit. Usability testing is a technique used in user-centered interaction design to evaluate a product by testing it on users. The results of the usability testing will show the effectiveness, efficiency and satisfaction with which specific to develop a RBM plan in the clinical trial unit. There are various types of Usability Testing which could involve focus groups or in-depth interviews with test users.

6: Perform routine evaluation and revision

After completion of the development and validation of the RBM, the Multi-Disciplinary Development Team should establish a schedule to review and alter the RBM tool as required by the clinical trial unit.

7.5 Direction for Future Research

Each phase of this thesis identified areas that require future research. This is summarised below:

- **Phase 1:** Risk based monitoring (RBM) tools for clinical trials: A systematic review.
  Future research direction: RBM tools for clinical trials are relatively new, their features and use vary widely, and they continue to evolve. This makes it difficult to identify the "best" RBM technique or tool. Therefore, equivalence testing is required to determine if RBM strategies directed by paper based and SaaS based RBM tools are comparable. Such research could be embedded within multi-centre clinical trials and conducted as a SWAT (Study within a Trial).

- **Phase 2:** Perceived barriers and facilitators to Risk Based Monitoring in academic-led clinical trials: a mixed methods study
  Future research direction: The cross-sectional nature of the research means that estimates of RBM implementation could only be assessed at one time point(214). It should also be noted that our study was conducted before the new ICH-GCP guidelines comes into effect on 14 June 2017(212). A longitudinal study should be conducted to

track RBM uptake over time and explore its impact on clinical trial conduct and monitoring outcomes. Such a study could use the results of the mixed methods study as baseline data.

- **Phase 3:** On-site and centralised monitoring – the TRUST study experience
  Future research direction: ICH GCP's emphasis on RBM is based on the assumption that it prevents wasting clinical trial resources, such as study budget and staff time, on monitoring activity that does not improve participant safety or data quality (24, 30, 131).The results of our document analysis suggest on-site and centralised monitoring are being used to complete the same recommended monitoring activities, thus leading to research wastage. Our study showed all centralised monitoring activity was being completed through on-site monitoring. However, further work is necessary to clarify the proportions of both centralised and on-site monitoring necessary to implement RBM effectively.

- **Phase 4:** Introducing Risk-Based Monitoring tools into academic-led clinical trial units in Ireland: a quality improvement intervention
  Future research direction: More in-depth research is needed to fully understand if the characteristics of a RBM tool impact on their usability. A qualitative study is needed to explore the results of the NASA TLX questionnaire. These results could be used by clinical researchers when developing their own RBM tools.

7.6 Conclusions

There is increasing recognition of the need to improve the quality and efficiency of clinical trials so that they can provide reliable and robust evidence needed by decision makers in health care who are faced by increasing demands and greater pressure on resources(149, 150, 222). This includes work to reduce waste in research, improve the selection of outcomes to measure and ensure that patients are more involved in all aspects of the trial(149, 222). Alongside this, the resources put into the monitoring of a trial need to be proportionate to the risks associated with that trial(110).

Risk-based monitoring (RBM) has disrupted the clinical trial industry, challenging conventional monitoring norms(110). It moves away from the traditional approach of

frequent on-site visits and 100% source data verification toward a combination of activities, including centralized data collection and monitoring(23). The concept of RBM implies that the chosen monitoring strategy is adapted to the local and trial-specific context(135). This means that a one-size-fits-all model is not possible(130). However, despite the availability of RBM tools and guidelines, challenges still exist with respect to clinical researchers establishing a local RBM process and implementing it in the desired way(29, 135).

Despite these challenges, RBM is now gaining acceptance as the preferred method of choice for monitoring clinical trials(23). Endorsed by regulators and leading industry forums, and further driven by escalating drug development costs and enabling technology shifts making data available real time, the clinical researchers are moving from a mode of resistance to acceptance(12, 141). The effective implementation of RBM requires delicately interweaving changes in technology, processes, people, and perspectives(141).

This thesis examined the multiple challenges that exist and proposed potential solutions to support RBM implementation. It adds to the current limited evidence base regarding the implementation of RBM into academic led clinical trials by responding to the call for interventions, such as the educational workshop, (chapter 4) to support RBM implementation(32). The choice of intervention option for this thesis was not clear at the outset. However, taking the time to explore the views of clinical researchers resulted in the development if QI intervention that was appropriate for the study population.

To conclude, the value of effective monitoring for clinical trials should not be underestimated and should be considered at the very early stages of trial design(156). Conducting clinical trials in resource-limited settings can be challenging, but careful planning and effective, well-conducted risk-based monitoring can assist in ensuring reliable and accurate scientific results while adhering to local and international guidelines and maintaining patient safety throughout(142, 244). However, there are still numerous challenges that lie ahead for RBM(201). First, individuals will have to

get comfortable with risk-based approaches(201). Training in RBM methodologies is a good first step, but practical experience will help refine RBM procedures over time.

Clinical researchers must be cautious when implementing RBM. This type of monitoring like traditional intensive on-site monitoring cannot correct the inherent problems in a clinical trial design or its implementation by a study team. Furthermore, the assumption that RBM can replace the need for on-site monitoring and improve participant safety or data quality has yet to be proven (26, 121). In 2017, the results of the Risk ADApted MONitoring (ADAMON) study were published(142). This study was a prospective, stratified, cluster-randomised, controlled study comparing extensive on-site monitoring with RBM in eleven clinical trials(142). The study found that compared with extensive on-site monitoring, the potential benefit of RBM was small and showed limited ability to identify systematic problems in the conduct of clinical trials. This finding is similar to the results of the TEMPER trial published in 2018, which retrospectively compared RBM to routine intensive onsite monitoring performed in three clinical trial trials(113). The TEMPER trial like the ADAMON trial, showed that RBM may be of potential use but needs improvement and that research into assessing the risks of a clinical trial is warranted before a gold standard RBM approach can be established. In addition, both the ADAMON study and the TEMPER trial found that that no monitoring strategy, be it RBM or traditional monitoring can correct deficiencies in a clinical trial design or conduct(113, 142). Therefore, it is imperative with RBM, that the monitoring approach should not exempt the sponsor or investigator from their responsibilities to develop and conduct high quality clinical trials. Even if the trial is considered 'low risk' participant safety must not be neglected, and the integrity of the trial must be upheld (129).

Appendix

Appendix A: Supplementary material for Chapter 2. Methods

Supplementary material 1. Knowledge Translation Frameworks

Table 23: Knowledge Translation Frameworks

Knowledge Translation Framework	Publication year	Description	Suitability
Coordinated Implementation Model (CIF)	1993	Model of research implementation that outlines the overall practice environment to capture schematically the competing factors of influence to the implementation process. CIF model demonstrates some of the additional and largely unexploited routes through which research information could influence clinical care. This model considers the views, activities, and available implementation instruments of at least four potential groups. Those include community interest groups, administrators, public policymakers, and clinical policymakers	Not suitable. This model requires the input of four different stakeholders and this thesis is only examining RBM from a clinical researcher's perspective(154)
The Ottawa Model of Research Use (OMRU)	1998	Developed within the context of continuity-of-care innovations. It is a 6-staged approach as follows: Set the Stage Specify the Innovation	Not suitable. This model does not include a process to support the sustainable of the intervention(252)

		Assess the Innovation, Potential Adopters and the Environment for Barriers and Facilitators Select and Monitor the Knowledge Translation Strategies Monitor Innovation Adoption Evaluate Outcomes of the Innovation	
The Promoting Action on Research Implementation in Health Services Framework (PARIHS)	1998	Framework proposes that successful implementation of research in practice is a function of the relation between the nature of the evidence, the context in which the proposed change is to be implemented and the mechanisms by which the change is facilitated The framework is expressed as: SI = f (E, C, F) where SI=successful implementation, E=evidence, C=context, F=facilitation and f=function of.	Not suitable. Not enough evidence on RBM to support the implementation of the PARIHS framework(253).
The Knowledge to Action (KNOWLEDGE TO ACTION) Process	2006	The KNOWLEDGE TO ACTION process has two components: (1) knowledge creation and (2) action. Each component contains several phases. The authors conceptualized the knowledge to action process to be complex and dynamic, with no definite boundaries between the two components and among their phases. The phases of the action component may occur sequentially or simultaneously, and the knowledge-creation-component phases may also influence the action phases.	Suitable: framework will support thesis aim and does not require previous RBM knowledge or multiple stakeholder involvement (151)
Stetler Model of Research Utilization	2001	This framework assesses how research findings and other relevant evidence can be applied in practice. The Stetler model of Research Utilization consists of five phases that guide: Phase 1: the selection of research evidence; Phase 2: formal utilization critique of studies;	Not suitable. Not enough evidence on RBM to support Phase 1 of this framework(254).

		Phase 3: consideration of research findings in the context of other forms of evidence, fit to the setting that is considering implementation, alignment with current practice and feasibility of adoption; Phase 4: the type of use decision and specifics of implementation; and Phase 5: dynamic evaluation, the details of which depend on the use decision.(254)	
Critical Realism and the Arts Research Utilization Model (CRARUM)	2009	CRARUM combines critical realism and arts-based methodologies. Critical realism facilitates understanding of clinical settings by providing insight into the interrelationship between its structures and potentials, and individual action. The arts-based methodology fosters reflection on the ways in which contextual factors influence and shape clinical practice, and how they may facilitate or impede change. The combination of critical realism and the arts within the CRARUM model promotes the successful embedding of interventions, and greater impact and sustainability	Not suitable. Arts –based methodology not appropriate for study population (255).
Consolidated Framework for Implementation Research (CFIR)	2009	CFIR is a conceptual framework used to guide the systematic assessment of multilevel implementation contexts to identify factors that might influence intervention implementation and effectiveness.	Not suitable-this framework is used to support the implementation of an intervention and not to guide its development.(256)
Theoretical Domains Framework (TDF)	2012	The TDF framework consists of 12 theoretical domains) groups of constructs from theories of behaviour change) that can be considered when exploring influencing factors and designing interventions.	Not suitable – framework based on behavioural change theory which is beyond the scope of the thesis(257)

Normalised Process Theory	2010	NPT focuses on the work that individuals and groups do to enable an intervention to become normalised. There are four main components to NPT: coherence (or sense - making); cognitive participants (or engagement); collective action (work done to enable the intervention to happen); and reflexive monitoring for formal and informal appraisal of the benefits and costs of the intervention	Not suitable-this framework is used to support the implementation of an intervention and not to guide its development(258).
Diffusion of Innovation Theory	1962	The key elements in diffusion research are: **Innovation:** Any idea, practice, or object that is perceived as new by an individual or other unit of adoption could be considered an innovation available for study **Adopters:** individuals, but can also be organizations, within social networks, or countries. **Communication Channels:** Communication channels allow the transfer of information from one unit to the other **Time:** The passage of time is necessary for innovations to be adopted; they are rarely adopted instantaneously. **Social system:** There are many roles in a social system, and their combination represents the total influences on a potential adopter.	Not suitable- this framework requires an implementation period for knowledge users to adopt a new idea. The thesis has a strict time restriction which means this framework could not be implemented correctly in the thesis(259)

Appendix B: Supplementary material for Chapter 3. Systematic review

Supplementary material 2: Systematic review search results

Search Engine: Pubmed

Date: 20/02/2016

Term	Results
1. Clinical Trial[MeSH Major Topic]	43176
2. trial[Title/Abstract]	419952
3. randomised trial[Title/Abstract]	6641
4. randomized trial[Title/Abstract]	33132
5. randomised controlled trial[Title/Abstract]	13003
6. randomized controlled trial[Title/Abstract]	39420
7. control trial[Title/Abstract]	3729
8. controlled clinical trial[Title/Abstract]	9942
9. clinical research study[Title/Abstract]	141
10. clinical protocol[Title/Abstract]	1392
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	**448763**
12. risk[MeSH Major Topic]	26688
13. risk assessment[MeSH Major Topic]	21510
14. "risk assessment tool"	1043
15. risk factors[MeSH Major Topic]	973
16. risk analysis[Title/Abstract]	3498
17. #12 OR #13 OR #14 OR #15 OR #16	**30614**
18. monitoring	492712
19. risk-based monitoring[Title/Abstract]	26
20. data monitoring[Title/Abstract]	588
21. remote monitoring[Title/Abstract]	1060
22. statistical monitoring[Title/Abstract]	48
23. risk adapted on site monitoring	23
24. risk proportionate monitoring	30
25. on site monitoring[Title/Abstract]	168
26. clinical trial monitoring[Title/Abstract]	26
27. centralised monitoring[Title/Abstract]	8
28. centralized monitoring[Title/Abstract]	36
29. monitoring method[Title/Abstract]	988
30. monitoring strategy[Title/Abstract]	347
31. targeted monitoring[Title/Abstract]	56
32. monitoring technique[Title/Abstract]	816
33. "quality assurance"	64062
34. "quality management"	16620
35. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	**565626**

36. #11 AND #17	**1069**
37. #35 AND #36	**60**

Search engine: Embase

Date: 20/02/2016

Term	Results
1. **'clinical trial'**/mj ‘	17,113
2. 'trial':ab,ti	568,568
3. 'randomised trial':ab,ti	8,767
4. 'randomized trial':ab,ti	42,869
5. 'randomised controlled trial':ab,ti	17,651
6. 'randomized controlled trial':ab,ti	54,705
7. ' control trial':ab,ti	5,429
8. 'controlled clinical trial':ab,ti	12,847
9. 'clinical research study':ab,ti	197
10. 'clinical protocol':ab,ti	2,124
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	**579,595**
12. 'risk'/mj	56,486
13. 'risk assessment'/mj	30,816
14. 'risk assessment tool'	1,714
15. 'risk factor'/mj	40,826
16. 'risk analysis':ab,ti	5,600
17. **#12 OR #13 OR #14 OR #15 OR #16**	131,014
18. 'monitoring'	706,524
19. 'risk based monitoring':ab,ti	56
20. 'data monitoring':ab,ti	1,156
21. 'remote monitoring':ab,ti	1,781
22. 'statistical monitoring':ab,ti	74
23. risk AND adapted AND on AND site AND monitoring	38
24. risk AND proportionate AND monitoring	46
25. 'on site monitoring':ab,ti	226
26. 'clinical trial monitoring':ab,ti	49
27. 'centralised monitoring':ab,ti	8
28. 'centralized monitoring':ab,ti	51
29. 'monitoring method':ab,ti	1,355
30. 'monitoring strategy':ab,ti	457
31. 'targeted monitoring':ab,ti	69
32. 'monitoring technique':ab,ti	1,001
33. 'quality assurance'	35,784
34. 'quality management'	41,298
35. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	**774,530**
36. #11 AND #17	**6,201**
37. #35 AND #36	**321**

Supplementary material 3: Appraisal Checklist for Grey literature (AACODS) checklist

Author	**Authority** Are the authors of the article listed? **Yes/No**	**Accuracy** Does the item have a clearly stated aim or brief? **Yes/No**	**Coverage** Are any limits clearly stated? **Yes/No**	**Objectivity** Does the work seem to be balanced in presentation? **Yes/No**	**Date** Does the item have a clearly stated date related to content? **Yes/No**	**Significance** Is the item meaningful? **Yes/No**	**Score (1-6)**
Smith et al[169]	Yes	Yes	Yes	Yes	Yes	Yes	**6**
MRC/DH/MRHA [28]	Yes	Yes	Yes	Yes	Yes	Yes	**6**
Journot et al [260]	Yes	Yes	Yes	Yes	Yes	Yes	**6**
Transcelerate [26]	Yes	Yes	Yes	Yes	Yes	Yes	**6**
Yee et al [173]	Yes	Yes	Yes	No	Yes	Yes	**5**

Brosteanu et al [261]	Yes	Yes	Yes	Yes	Yes	Yes	**6**
Nordic Monitoring Network[27]	Yes	Yes	Yes	Yes	Yes	Yes	**6**
Swiss Clinical Trial Organisation[170]	Yes	Yes	Yes	Yes	Yes	Yes	**6**
Bioclinica[174]	Yes	Yes	No	Yes	Yes	Yes	**5**
DATATRAK[175]	Yes	Yes	No	No	Yes	Yes	**5**
ICON[176]	Yes	Yes	No	No	Yes	Yes	**5**
JMP[177]	Yes	Yes	No	No	Yes	Yes	**5**
Meditata[262]	Yes	Yes	No	No	Yes	Yes	**5**
xClinical[179]	Yes	Yes	No	No	Yes	Yes	**5**

Flex Databases[180]	Yes	Yes	No	No	Yes	Yes	**5**
Triumph Research Intelligence (TRI)[181]	Yes	Yes	No	No	Yes	Yes	**5**
Cyntegrity[172]	Yes	Yes	No	No	Yes	Yes	**5**
CluePoints[182]	Yes	Yes	No	No	Yes	Yes	**5**
Remarque Systems[183]	Yes	Yes	No	No	Yes	Yes	**5**
Algorics[184]	Yes	Yes	No	No	Yes	Yes	**5**
Kestrel Biologic[185]	Yes	Yes	No	No	Yes	Yes	**5**
Clindata[186]	Yes	Yes	No	No	Yes	Yes	**5**
Clinerion [187]	Yes	Yes	No	No	Yes	Yes	**5**

ERT[188]	Yes	Yes	No	No	Yes	Yes	**5**

Appendix C: Supplementary material for Chapter 4

Supplementary material 4: Survey questionnaire

Monitoring Survey

Welcome to My Survey

Clinical trial monitoring is mandatory under ICH-GCP guidelines. In June 2015, the ICH published the Integrated Addendum to ICH GCP, which recommends systematic, prioritised, risk-based monitoring for clinical trials.

The aim of this survey is:

- To identify how academic led clinical trials are monitored in Ireland.
- To better understand the reasons for using the methods identified.
- To identify any limitations of these methods.

1. Please indicate if you consent for your answers to be used for research purposes
   Yes ☐ No ☐

Please enter your contact details below. This information will be used to track the survey's response rate

2. Name: _____

3. Address: _____

Demographics

4.1 Please indicate the University/Clinical trial unit you are affiliated with?

- University College Cork (UCC)
- National University of Ireland Galway (NUIG)
- Wellcome Trust -HRB Clinical Research Facility at St. James Hospital
- Royal College of Surgeons Ireland (RCSI)
- University College Dublin (UCD)

* 4.2 What is your role within a clinical trial?

- Principal Investigator (PI)
- Clinical trial nurse
- Project Manager
- Quality Manager
- Study doctor
- Study Monitor
- Biostatistics
- Pharmacists

Other (please specify) _____

* 4.3 Please identify the Medical Therapeutic area/areas in which you work? (i.e. Neurology, Oncology, Geriatrics)

4.4 How many years have you been working in clinical trial research?

- **<1**
- **1-3**
- **4-6**
- **>6**

4.5 Please list any specific clinical trial training that you have received? (I.e. GCP training, postgraduate training)

4.6 Since the introduction of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulation in 2004, have you conducted international multi-site trials?

Yes ☐ No ☐

4.7 Since the introduction of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulation in 2004, how many of the following types of clinical trials have you conducted? ** Regulated trials need HPRA approval

	0	**1**	**2-3**	**>3**
Industry/commercial-led, regulated clinical trial				
Academic-led, regulated clinical trial				
Non-regulated clinical trials				

* 4.8 Since 2004, have you participated in a HPRA/ IMB clinical trial inspection?

Yes ☐ No ☐

On-site monitoring

* 5.1 Do you think the following features of a clinical trial are important to consider when deciding the frequency of on-site visits required to monitor the trial?

	Very important	Moderately important	Not important
Investigational Medicinal Product (IMP)			
Budget			
Study population			
Phase of trial (I, II, III, and IV)			
Experience of clinical trial team			

5.2 Which of the following factors would you use to trigger an onsite monitoring visit? (Select all that apply)?

Several protocol deviations	
Incidence of adverse events	
Upcoming regulatory inspection	
Low recruitment rate	
Inexperience of clinical trial site	
High subject drop-out rate	

Other (please specify)_____

Centralised monitoring

****Centralised monitoring is also known as remote monitoring. This monitoring system allows clinical researcher to remotely monitor clinical trial activity such as recruitment trends, data entry etc.**

6.1 Does your clinical research unit have a SOP for centralized monitoring?

Yes ☐

No ☐

Not sure ☐

6.2 Since 2004, have you used centralised data monitoring for the following quality management activities in a clinical trial?

	Yes	**No**	**Not sure**
To assess protocol compliance			
To completely replace on-site monitoring			
To supervise study recruitment			
To record pharmacovigilance information (I.e. adverse events, SAEs)			
To organise sampling and material logistics (e.g. specimen collection, storage and shipment)			
To inspect the informed consent process			
To identify missing data			

* 6.3 Please indicate how important you consider the following factors to be as a barrier to implementing centralised monitoring in clinical trials?

	Very important	Moderately Important	Not important
Lack of education and training in centralised monitoring			
Cost associated with centralised monitoring			
IT demands of centralised monitoring			
Workload associated with centralised monitoring			

Risk Based Monitoring

7.1 Please name the most clinical trial you worked on?

_____

7.2 In this clinical trial did you or your study team complete an assessment of risk prior to developing the monitoring plan?

Yes - if **Yes** please **only** answer questions **8.1-8.4**

No - if **No** please **only** answer questions **9.1-9.3**

Not sure - if **Not sure** please **only** answer questions **10.1-10.2**

Note: These questions are only relevant to participants that answered 'Yes' to question 7.2 In this clinical trial did you or your study team complete an assessment of risk prior to developing the monitoring plan?

8.1 Did you or your study team use a risk assessment tool when assessing the risks in your clinical trial? **a risk assessment tool is used to identify the risks within an approved clinical trial protocol that can be mitigated through monitoring. For example, a risk assessment tool could be an in-house SOP, a checklist or a computer programme**

Yes ☐

No ☐

Not sure ☐

8.2 Please indicate why you or your study team performed a risk assessment? (Select all that apply)

To fulfil HPRA/IMB requirements	
To improve patient safety	
To improve data accuracy	
To reduce monitoring costs	
To determine a schedule for on-site monitoring visits	
To fulfil GCP requirements	
Not sure	

Other _____

8.3 Do you think the following are important features of a risk-assessment tool?

	Very important	**Moderately Important**	**Not important**
It is GCP compliant			
Training is required to operate the tool			
It is approved by the HPRA			
It requires specialised software to operate			
It is paper based			
It contains less than 20 risk assessment questions			
It has been formally validated for precision			

It clearly defines risk and appropriate monitoring guidelines			

8.4 Since 2004, have you implemented a risk-based monitoring plan in a clinical trial?

Yes ☐

No ☐

I am not familiar with the term risk-based monitoring ☐

Note: These questions are only relevant to participants that answered 'No' to question 7.2 – *In this clinical trial did you or your study team complete an assessment of risk prior to developing the monitoring plan?'*

* **9.1** Please indicate why you or your study team did not perform a risk assessment? (Select all that apply)

It is not a GCP requirement	
Do not have the expertise to perform a risk assessment	
It is too time consuming	
It is too expensive	
It will not improve patient safety	
Not sure	

Other _____

9.2 Do you think the following are important features of a risk-assessment tool? **a risk assessment tool is used to identify the risks within an approved clinical trial protocol that can be mitigated through monitoring. For example, a risk assessment tool could be an in-house SOP, a checklist or a computer programme**

	Very important	**Moderately Important**	**Not important**
It is GCP compliant			
Training is required to operate the tool			

It is approved by the HPRA			
It requires specialised software to operate			
It is paper-based			
It contains less than 20 risk assessment questions			
It has been formally validated for precision			
It clearly defines risk and appropriate monitoring guidelines			

9.3 Since 2004, have you implemented a risk-based monitoring plan in a clinical trial?

Yes ☐

No ☐

I am not familiar with the term risk-based monitoring ☐

Note: These questions are only relevant to participants that answered 'Not sure' to question 7.2 –*'In this clinical trial did you or your study team complete an assessment of risk prior to developing the monitoring plan?*

10.1 Do you think the following are important features of a risk-assessment tool? **a risk assessment tool is used to identify the risks within an approved clinical trial protocol that can be mitigated through monitoring. For example, a risk assessment tool could be an in-house SOP, a checklist or a computer programme**

	Very important	**Moderately Important**	**Not important**
It is GCP compliant			
Training is required to operate the tool			
It is approved by the HPRA			
It requires specialised software to operate			
It is paper-based			
It contains less than 20 risk assessment questions			

It has been formally validated for precision			
It clearly defines risk and appropriate monitoring guidelines			

10.2 **Since** 2004, have you implemented a risk-based monitoring plan in a clinical trial?

Yes ☐

No ☐

I am not familiar with the term risk-based monitoring ☐

Supplementary material 5: Topic guide for semi structured questionnaires

Study: Implementation of risk-based monitoring in academic led Irish clinical trials

Document: Interview Topic Guide

Hi (participant's name) , thank you for completing the Monitoring Survey. The questions I will ask you today will further explore your view and opinions on risk-based monitoring. There are no right answers so please stop me if you want me to clarify any question.

---

1. To start could you tell me about the most recent clinical trial you worked on and your role in that trial?
2. At what stage is that trial- recruitment, close out?
3. How is/was that trial monitored?
4. Did you/team use on-site and/or centralised monitoring? Did you use an electronic clinical report form eCRF?
5. Who developed the initial monitoring plan? *(You, monitor, PI)*
6. Were you involved in the development of the monitoring plan?
7. Why did you/they choose this type of monitoring? *(Cost, IT, staff)*
8. Was the monitoring plan reviewed and changes during the trial duration?
9. In November 2016, the ICH-GCP will launch the updated version of GCP which will recommend clinical trial Sponsors use risk based monitoring. Are you familiar with the new guideline?
10. If no, we can review paragraph from 'participant sheet'?
11. Are you familiar with the term risk-based monitoring?
12. Have you ever conducted risk-based monitoring in a clinical trial?
13. Do you think risk based monitoring will change you monitor a clinical trial in the future?
14. Do you feel there are benefits associated with RBM?

15. Do you think there are limitations associated with RBM?

16. In future trials you work on, would you consider using risk-based monitoring?

17. In these trials, would you like to be involved in the development of a monitoring plan?

18. Do you feel you have the skills and knowledge base to conduct RBM?

19. What intervention or support would help you conduct risk-based monitoring?

20. Who should lead this intervention?

21. How much commitment would you give to the intervention?

22. Do you have any additional information you would like to add?

23. Do you have any questions for me?

Appendix D: Supplementary material for Chapter 5

Supplementary material 6: Automatic and manual central monitoring queries from the TRUST Thyroid Trial

Table 24. Automatic and manual queries

Automatic data queries
1. Participants concomitant medication
2. Participants eligibility
3. Missed or delayed participant visits
4. Data entry errors
5. Dispense Medication
6. Participant withdrawal procedure
7. Delayed study tests such as blood samples
8. Missing barcodes on blood work
9. Inaccurate study test results
Manual data queries
9. Missed or delayed participant visits
10. Data entry errors
11. concomitant medication

Appendix E: Supplementary material for Chapter 6

Supplementary material 7: Protocol for quality improvement study
Protocol - RBM tool usability study

Version 1 – 27/02/2017

Factors that determine the selection of a Risk Based Monitoring (RBM) tool in academic (Investigator led) clinical trials

Aim: Select an operational Risk Based Monitoring (RBM) tool for use in academic led clinical trials

Background

In November 2016, the ICH published the integrated addendum to ICH-GCP E6 (R2), advising Sponsors to develop a systematic, prioritised, risk-based approach to monitoring clinical trials. This process is more commonly known as risk-based monitoring (RBM). It incorporates both centralised monitoring conducted off-site through an examination of electronic trial data and on-site monitoring practices that are proportional to the risks associated with the clinical trial. These risks relate to the Investigational Medicinal Product (IMP), the study population and the robustness of the study design. For example, in high-risk trials RBM may involve 100% source data verification (SDV) onsite monitoring while for low-risk trials it may include 80% SDV through centralised and on-site monitoring practices. Moreover, once a trial starts, sponsors must continuously review the risk profile of a trial while it is on-going and modify monitoring practices accordingly. In 2013, the Organisation for Economic Co-operation and Development (OECD) published guideline which advised clinical researchers to use a RBM tool when developing their RBM plan. Such tools should have two functions, firstly they must support the assessment of risk in a clinical trial

protocol and secondly, they should provide guidance for subsequent monitoring activity that can mitigate the risk identified.

Project Context

In 2016, I published a systematic review which identified 24 RBM tools that met the OECD's criteria: https://www.ncbi.nlm.nih.gov/pubmed/27641969 .They differed in terms of mode of administration (paper based versus software as a system (SAAS), baseline risk assessment process and guidance for on-site and centralised monitoring. However, I did not find a gold standard or validated RBM approach.

To help overcome this challenge, I applied the findings of my systematic review to the ICH-GCP and OECD guideline to develop four criteria to consider when choosing a RBM tool.

These are:

1. Ensure the RBM tool's baseline risk assessment process examines the risk indicators set out in the Risk indicator taxonomy for supervision of clinical trials on medicinal products.

2. Ensure the RBM tool can support both on-site and centralised monitoring. For SaaS tools ensure that on-site monitoring data can be entered manually into the system

3. Ensure the RBM tool provides a process for systematic review of the trial's risk profile

4. Ensure the RBM tool is cost efficient i.e. the paper-based tools are available free of charge however they need the support of an Electronic Data Capture (EDC) system to perform centralised monitoring.

Subsequently three of the 24 RBM tools I identified fulfilled my 4 recommendations listed above. These tools are freely available for use my clinical researchers.

RBM tools include:

Nordic Monitoring Centre - Risk Assessment Tool

Swiss Clinical Trial Organisation – Risk Assessment Form

TransCelerate – Risk Assessment and Categorisation Tool (RACT)

Note: Each tool must be completed by a clinical trial team including quality and clinical staff.

Project Aim: To test the usability of the three RBM tools listed above and select a suitable one for use in academic led trials in UCC, NUIG and RCSI.

Methods

Study Design: Usability testing

* N.B Usability testing refers to evaluating a product or service by testing it with representative users. It is more commonly used in software development

Data Collection:

Quantitative data: Results from the NASA Task Load Index (NASA-TLX) questionnaire, the time taken to complete each RBM tool.

NASA-TLX is a widely used, subjective, multidimensional assessment tool that rates perceived workload in order to assess a task, system, or team's effectiveness or other aspects of performance. It was developed by the Human Performance Group at NASA's Ames Research Center over a three-year development cycle that included more than 40 laboratory simulations.

NASA-TLX originally consisted of two parts: the total workload is divided into six subscales that are represented on a single page https://en.wikipedia.org/wiki/NASA-TLX#/media/File:NasaTLX.png

Six subscales are: Mental Demand, Physical Demand, Temporal Demand, Performance, Effort and Frustration. Each subscale is rated for each task within a 100-

points range with 5-point steps. These ratings are then combined to the task load index. Providing descriptions for each measurement can be found to help participants answer accurately. These descriptions are as follows:

- **Mental Demand**

How much mental and perceptual activity was required? Was the task easy or demanding, simple or complex?

- **Physical Demand**

How much physical activity was required? Was the task easy or demanding, slack or strenuous?

- **Temporal Demand**

How much time pressure did you feel due to the pace at which the tasks or task elements occurred? Was the pace slow or rapid?

- **Overall Performance**

How successful were you in performing the task? How satisfied were you with your performance?

- **Frustration Level**

How irritated, stressed, and annoyed versus content, relaxed, and complacent did you feel during the task?

- **Effort**

How hard did you have to work (mentally and physically) to accomplish your level of performance?

Setting: The study will be conducted in four academic Clinical Research Facilities in Ireland

Study population: Quality Managers, Monitors, Research Nurses, Sponsor medic, data manager, biostatistician- staff usually involved in developing monitoring plans.

Usability Testing – Standard Operating Procedure (SOP)

Procedure

1. Assemble your 'MDTT'. This is the team who normally develop, write, review and approve monitoring plans at your institution. The MDTT may include Monitors, Quality Managers, Research Nurses, Sponsor Medic Data Managers, biostatisticians – the composition of the MDTT may be different at different sites depending on local practice. Document the members of your MDTT indicating their role (e.g. monitor, quality manager etc.).

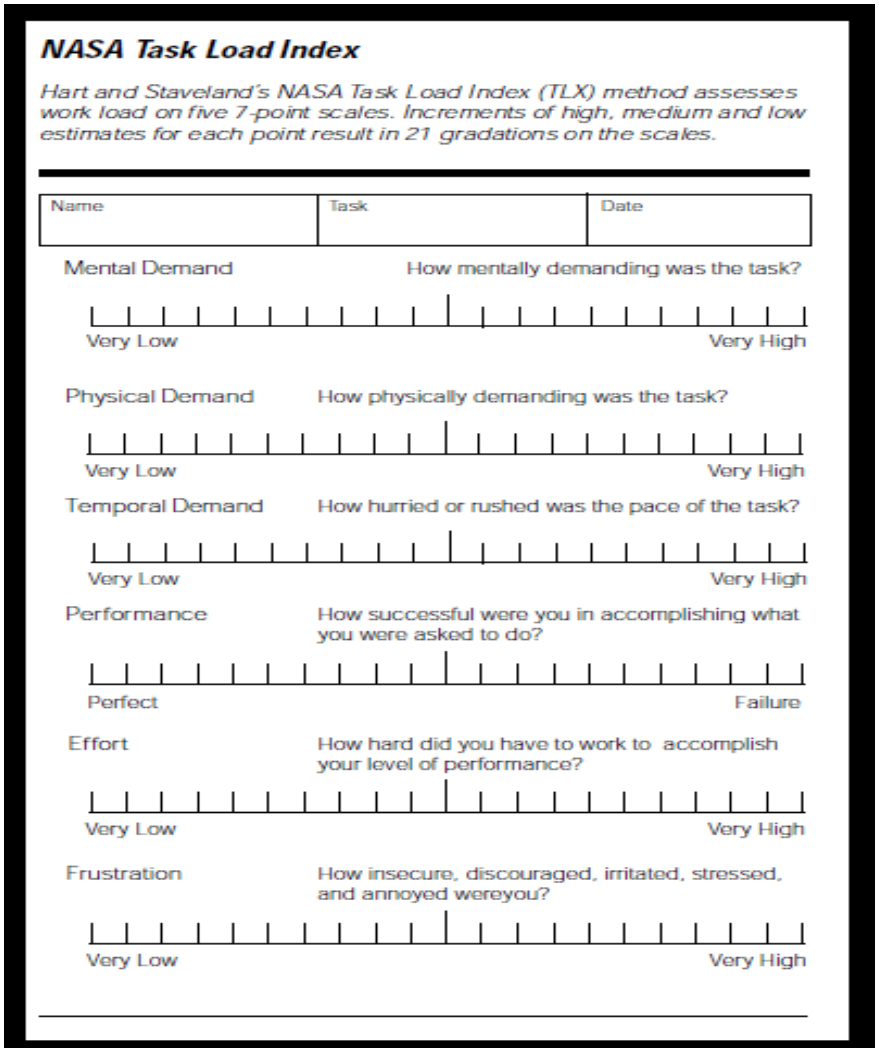
2. Select a clinical trial protocol you wish to use for the Usability testing. These protocols should pertain to clinical trials of Investigational Medicinal Products (IMP) that are or were sponsored by your organisation. The clinical trial phase is not significant. However, where possible please use the version of the protocol that was in use at study start-up. Document the protocol version, name, clinical trial phase, and IMP for each protocol.

3. Arrange a time and date for the members of your MDTT to meet and collectively apply the 3 RBM tools to each of the three clinical trial protocols. This gives a total of 3 assessments. This step will involve the MDTT completing the RBM tools with data from the respective protocol. This process will result in the identification of a risk classification for each clinical trial and corresponding monitoring guideline on how each risk should be mitigated through on-site and/or centralised monitoring.

4. After you have applied each of the 3 RBM tools independently to each protocol, please complete a NASA TLX questionnaire to record the usability of each RBM tool.

5. In February 2018, MDTTs will be asked to complete a short questionnaire to establish if they have introduced one or more of the RBM tools into their organisation.

Supplementary material 8: NASA Task Load Index (NASA TLX)



NASA Task Load Index

Hart and Staveland's NASA Task Load Index (TLX) method assesses work load on five 7-point scales. Increments of high, medium and low estimates for each point result in 21 gradations on the scales.

Name	Task	Date

Mental Demand — How mentally demanding was the task?

Very Low — Very High

Physical Demand — How physically demanding was the task?

Very Low — Very High

Temporal Demand — How hurried or rushed was the pace of the task?

Very Low — Very High

Performance — How successful were you in accomplishing what you were asked to do?

Perfect — Failure

Effort — How hard did you have to work to accomplish your level of performance?

Very Low — Very High

Frustration — How insecure, discouraged, irritated, stressed, and annoyed wereyou?

Very Low — Very High

Supplementary material 9: The Template for Intervention Description and Replication (TIDieR) checklist

Item no.	Item	QI Intervention
	Brief name	
1.	**Provide the name or a phrase that describes the intervention.**	Introducing Risk-Based Monitoring tools into academic-led clinical trial units in Ireland: a quality improvement intervention
	Why	
2.	**Describe any rationale, theory, or goal of the elements essential to the intervention**	At the time the intervention was developed and implemented, the use of RBM tools by academic clinical researchers in Ireland was low and lack of education and training was the main barrier to RBM tool use. The intervention is an education QI intervention. The aim of this study was to develop, implement and evaluate an educational Quality Improvement (QI) intervention. Educational QI intervention provide an opportunity for participants to increase their knowledge or understanding of a specific topic and by doing so allows the mechanism to drive behaviour change. The educational QI intervention in this study aimed to teach academic clinical researchers in Ireland about RBM tools and by doing so change their monitoring behaviour and support them to use RBM tools when developing monitoring plans for their clinical trials.
	What	
3	**Materials: Describe any physical or informational materials used in the**	The physical material used in the intervention included paper based RBM guidelines, RBM tools and paper-based outcome questionnaires.

	intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	1. Paper based RBM guidelines • Purpose: To educate participants on the fundamental concepts of RBM to ensure they had enough baseline knowledge required to work the RBM tools. • Guideline used and rationale for its selection ▪ Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (18) This guideline provides the premise for RBM and explains what clinical trial regulators will expect to see in a RBM plan. ▪ OECD Recommendation on the Governance of Clinical Trials (10) This guideline was the first and only document to define and explain the characteristics of a RBM tool. ▪ Risk indicator taxonomy for supervision of clinical trials on medicinal products (125) First peer reviewed paper explaining the risk assessment process of involved in RBM and identified and categorized I risk indicators that may present an elevated safety and/or ethical risk for participants, and/or for data in a clinical trial.

		2. RBM tools Purpose: interactive education session to educate the participants on the components of a RBM tool and how to apply the RBM tool to a study protocol to develop a RBM plan ▪RBM tool and rationale for its inclusion in the QI intervention The QI intervention included three paper based RBM tools the Risk Assessment Tool (RAT) (22), Risk assessment for risk adapted monitoring (RARAM) (159) and the Risk Assessment Categorisation Tool (RACT) (20) Each of the three RBM tools included in the QI intervention fulfilled four criteria for a RBM tools. They each assessed risks in accordance with the Risk Indicator Taxonomy for supervision of clinical trials on medicinal products. They supported both on-site and centralised monitoring and provided a process to systematically review trial's risk profile. Finally, each tool was cost efficient as cost as they were freely available on the internet. 3. Outcome questionnaires Purpose: To evaluate the outcome of the QI intervention – first to assess the usability of the RBM tools and secondly to determine if the intervention supported the participants to change their monitoring behaviour and use RBM in their clinical trials. Questionnaires and their selection

		▪NASA Task Load (NASA-TLX) questionnaire – is a paper-based questionnaire that measured the measured workload of a task. After each MDTT applied the three RBM tools to their selected clinical trial protocol, they completed three NASA-TLX questionnaires, each questionnaire measured the perceived workload associated with each RBM tool included in the QI intervention. ▪Utilization Scale questionnaire - used to measure how much, if any, the MDTT's had used the knowledge they gained in the QI intervention and implemented the RBM tools in their clinical trial units. Six months after participating in the QI intervention, the four Quality and Regulatory Affair Managers from each MDTT, one from each clinical trial unit, were asked to complete a Utilization Scale questionnaire The Quality and Regulatory Affair Managers were the only members of each MDTT asked to complete this questionnaire because they coordinate clinical trial monitoring in their clinical trial unit.
4	**Procedures: Describe each of the procedures, activities, and/or processes used in the intervention including any enabling or support activities.**	The procedures in the QI intervention were rolled out in four stages listed below. Stage 1: Introduction / baselined RBM education session - face to face workshop Stage 2: RBM tool application - face to face workshop Stage 3: Evaluation Stage 4: Follow up
	Who provided	
5	**For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.**	The intervention was developed by an expert panel of clinical trial experts. The expert panel consisted of seven clinical trial experts which included a trial sponsor (1), principle investigators (2), trial coordinator (1), quality manager (1) and a trial doctor (1) and a clinical trial monitor (1). All panel members had a minimum of five years and

		maximum of twenty years' experience of developing and implementing clinical trial monitoring plans.
	How	
6	**Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.**	The QI intervention was delivered through a face to face intervention workshop. The Intervention was facilitated by one researcher who delivered the intervention in the same format for each of the four Multi -Disciplinary Testing Teamss (MTDDs).
	Where	
7	**Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features**	The QI intervention was delivered in four academic run clinical trial units in Ireland based in publically funded hospitals. Each of the four clinical trial units deliver research across numerous clinical specialties including oncology, cardiology, neurology, ophthalmology and neonatal research in accordance with the EU Clinical Trials Directive and the new ICH GCP guideline (56). At the time of the QI study, none of the units used a RBM tool and none had conducted RBM. Each clinical trial unit assembled a Multidisciplinary Testing Team (MDTT). For this study, we defined a MDTT as a collection of members within each clinical trial unit who normally develop, write, review and approve monitoring plans for trials that their clinical trial unit manages. In

		total, the four MDTTs consisted of 12 participants; study doctor (n=1), quality and regulatory affair managers (n=4), clinical trial monitors (n=5) and research nurses (n=2).
	When and How Much	
8	**Describe the number of times the intervention was delivered and over what period including the number of sessions, their schedule, and their duration, intensity or dose.**	The intervention was delivered once to each of the four MDTTs. The intervention lasted approximately two hours.
	Tailoring	
9	**If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.**	All MDTTs received the same intervention
	Modifications	
10	**If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).**	The intervention was not modified during the study. The intervention was delivered in the same sequence for each of the MDTTs.
	How Well	
11	**Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.**	The trial fidelity was not formally assessed however, the intervention was delivered as planned Facilitated by the fact that the intervention was a simple and not a complex intervention The members of each MDTTs were comparable in terms of academic background and clinical trial experience. Thus, the intervention did not have to be tailored to address the needs of individual MDTTs. Therefore, the objectives of the intervention was consistent for each MDTT and delivered as planned.

12	**Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.**	N/a – see comment above

Appendix F. Research training undertaken during doctoral research

Postgraduate courses	
June 2017	Postgraduate Diploma in Clinical Trials University of Edinburgh (online)
May 2017	Certificate in Biomedical Device Manufacture Cork Institute of Technology (CIT)
May 2015	Postgraduate Certificate in Clinical Trials University of Edinburgh (online)
UCC Postgraduate modules	
2015	PG6003: Teaching and Learning assignment
2015	PG6009: Graduate Information Literacy Skills
2015	PG6001: STEPS - Scientific Training for Enhanced Postgraduate Study
2016	PG7021: An Introduction to the Ethics of Health Research
2016	PG6025: Community - Based Participatory Research
2016	PG6008: Qualitative Data Analysis and Computer Assisted Qualitative Data Analysis Software for the Social Sciences and Humanities
Clinical trial courses	
April 2017	Clinical investigation of medical devices for human subjects –ISO 14155 HRB Clinical Research Facility Cork
December 2016	Good Clinical Practice (GCP) Course HRB Clinical Research Facility Cork

Appendix G. Prizes and awards relating to doctoral research

September 2016	Best speaker award at the Irish Centre for Fetal and Neonatal Translational Research (INFANT) Research Day 2016

Appendix H. Dissemination of doctoral research

Supplementary material 9: Peer reviewed PhD publications and links to papers

- Hurley C, Shiely F, Power J, Clarke M, Eustace JA, Flanagan E, et al. Risk based monitoring (RBM) tools for clinical trials: A systematic review. Contemporary clinical trials. 2016;51:15-27. *https://www.ncbi.nlm.nih.gov/pubmed/27641969*

- Hurley C, Sinnott C, Clarke M, Kearney P, Racine E, Eustace J, et al. Perceived barriers and facilitators to Risk Based Monitoring in academic-led clinical trials: a mixed methods study. Trials. 2017;18(1):423. *https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2148-*

Conference proceedings – oral presentation

September 2015	Risk based monitoring. The Health Research Board- Trial Methodology Research Network – 3rd Annual Trial Methodology Symposium, Dublin
September 2016	Best speaker award at the Irish Centre for Fetal and Neonatal Translational Research (INFANT) Research Day 2016
October 2017	Risk based monitoring. The Health Research Board- Trial Methodology Research Network – 3rd Annual Trial Methodology Symposium, Dublin
May 2018	Perceived barriers and facilitators to Risk Based Monitoring in academic-led clinical trials: a mixed methods study. Society for Clinical Trials, 39th Annual Meeting, Oregan USA

Conference proceedings: poster presentations

2015	HRB Trials Methodology Research Network (HRB-TMRN), Cork
2015	3rd International Clinical Trials Methodology Conference, Glasgow
2016	SCT 37th Annual Meeting (2016) - Society for Clinical Trials (SCT), Montreal
2016	Irish Research Nurses Network, Dublin
2016	SPHeRE 'Structured Population and Health-services Research Education' Conference, Dublin

Appendix I. Additional academic activity during the conduct of this research

Webinar

September 2016	Risk based monitoring and the introduction of the new ICH-GCP guideline for the Health Research Board – Trial Methodology Research Network (HRB-TMRN)

Teaching

2015	Tutor for Introduction to Health Statistics module on the BSc in Public Health Sciences UCC
2015	Tutor on the Data Management for Public Health module as part of the BSc in Public Health Science
2016	Tutor for Introduction to Health Statistics module on the BSc in Public Health Sciences UCC
2016	Tutor on the Data Management for Public Health module as part of the BSc in Public Health Science
2016	Thesis Tutor for the Master's in Public Health (MPH)

Research funding awards

September 2014	Strategic Research Fund PhD Scholars Programme, University College Cork **Awarded** €45000 to pay for my student fees and stipend
September 2015	Doctoral Travel Bursary, University College Cork **Awarded** €1000 to attend the conference in Montreal

May 2016	Study Within a Trial Study (SWAT) funding, Health Research Board-Trial Methodology Network (co-applicant) **Project awarded** €10000 to conduct a conduct a SWAT titled - Patients' perspectives and preferences on clinical trial dissemination: the TRUST Thyroid trial experience

Peer reviewer

2016	*BMC Medical Research Methodology, j*ournal
2017	*Trials* – journal

Co-author papers on clinical trial and clinical trial methodology

- Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RG, Mooijaart SP, **Hurley C** et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. **New England Journal of Medicine**. 2017. https://www.nejm.org/doi/full/10.1056/NEJMoa1603825

- Stott DJ, Gussekloo J, Kearney PM, Rodondi N, Westendorp RG, Mooijaart S, **Hurley C** et al. Study protocol; Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism-a randomised placebo controlled Trial (TRUST). BMC endocrine disorders. 2017;17(1):6. https://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-017-0156-8

- Racine E, **Hurley C** et al. Study within a trial (SWAT) protocol. Participants' perspectives and preferences on clinical trial result dissemination: The TRUST Thyroid Trial experience. Contemporary Clinical Trials Communications. 2017. *https://www.sciencedirect.com/science/article/pii/S2451865417300479*

- Racine E, **Hurley C**, Cheung A *et al.* Participants' perspectives and preferences on clinical trial result dissemination: The TRUST Thyroid Trial experience. *HRB Open Res* 2018, 1:14
  https://hrbopenresearch.org/articles/1-14/v1

Poster

- Siobhan Browne, Kenneth Burns, Rebecca Dennehy, Ruth Hally, Caroline Hurley, Blazej Kauca, Aine Kearns, Catherine O'Mahony, Katarzyna Pyrz, Sarah Robinson, Kieran Walsh. Building RRI Proficiency through a Community-Based Participatory Research Module. *7th Living Knowledge Conference.*

  https://www.researchgate.net/publication/304659058_Building_RRI_Proficiency_through_a_Community-Based_Participatory_Research_Module

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