Integrated Rapid-Cycle Comparative Effectiveness Trials Using Flexible Point of Care Randomisation In Electronic Health Record Systems

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Abstract

Whilst the Randomised Controlled Trial remains the gold standard for deriving robust causal estimates of treatment efficacy, too often a traditional design proves prohibitively expensive or cumbersome when it comes to assessing questions regarding the comparative effectiveness of routinely used treatments. As a result, patients experience variation in practice as clinicians lack the evidence needed to personalise treatments effectively. This variation may be classified as unwarranted, where existing evidence is ignored, or legitimate where in the absence of evidence, clinicians rely on experience, expert opinion, and inferred principles from basic science to make decisions.

We argue that within the right ethical and technological framework, legitimate variation can be transformed into a mechanism for evidence generation and learning. Learning Health Systems which harness existing variation in practice, represent a novel approach for generating evidence from everyday clinical practice. The development of these systems has gained traction due to the increased availability of modern Electronic Health Record Systems. However, despite their promise, overcoming hurdles to successfully integrating clinical trials within Learning Health Systems has proven challenging.

This article describes the origins of integrated clinical trials and explores two main barriers to their further implementation - how best to obtain informed consent from patients to participate in routine comparative effectiveness research, and how to automate and integrate randomisation into a clinical workflow. Having described these barriers, we present a potential solution in the form of a research pipeline using a novel form of flexible point-of-care randomisation to allow clinicians and patients to participate in studies where there is clinical equipoise.

Statement of Significance

Problem:	*Many routine treatments lack a strong evidence base. Where evidence is weak or non-existent, clinicians vary their practice and patients receive differing care. Current randomised trial designs are too expensive and impractical to conduct routine Comparative Effectiveness Research at scale.*
What is already known:	*The clinically integrated trial design offers an opportunity to embed research into clinical practice, but so far has been limited in its application.*
What this paper adds:	*This special commentary reviews the current state of the art of clinically integrated trial designs, highlights the outstanding barriers to implementation, and proposes a novel trial pipeline taking advantage of a fully embedded informatics approach, together with a flexible approach to treatment randomisation at the point of care.*

Statement of Significance

Introduction

Randomised Controlled Trials (RCTs) are the optimal way of demonstrating treatment efficacy in homogenised cohorts, under strict treatment protocols [1]. However, the 'classical' RCT, described by Granholm et al. as a "parallel, two-group, fixed-allocation ratio RCT analysed with frequentist methods" (p165), may be inadequate when it comes to answering questions which judge the effectiveness of treatments across heterogeneous patient groups, under pragmatic conditions [2].

Evaluations of routine treatment strategies are classed as Comparative Effectiveness Research (CER), defined by the Institute of Medicine as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care" (p203) [3]. This was in response to the identification of widespread variations in care across the United States. Learning about the effectiveness of routine treatment strategies was prioritised, with over $ 1 billion of federal funding allocated as a result [4].

This renewed focus accompanied innovations in pragmatic trial design which sought to address some of the limitations of the classical RCT approach. Cluster randomised designs, although conceptually dating back to the early 1900s, have become increasingly popular for pragmatic trials in healthcare, particularly for the evaluation of system wide processes, where randomisation at the individual level would be problematic [5,6]. This design confers good generalisability, as all patients in a cluster are enrolled, also improving efficiency, and lowering costs. Through incorporating cross-over periods for intervention exposure, issues such as time dependent confounding, and the Hawthorne effect are ameliorated, and randomising cluster exposure can help maintain blinding [7].

Interventions may also be evaluated across clusters in a graduated fashion. Stepped wedge cluster randomised trials are highly pragmatic and acknowledge the logistical difficulties in simultaneously rolling out and evaluating system level interventions [8]. However, despite the advantages of cluster randomisation for pragmatic trials, these studies remains vulnerable to selection bias, either through foreknowledge of allocation (resulting from potential inability to blind treatment allocation), or through differential recruitment rates within clusters (which may dilute treatment effects) [9]. In addition, clinicians within each cluster must embrace a collective "group equipoise" for participation, otherwise there may be variability in treatment application within a cluster. Although this may be countered by an intention to treat approach to the analysis, when it comes to discerning individual treatment effects, this may not be the ideal approach [10].

Efforts to improve trial efficiency further have yielded additional study designs capable of evaluating several treatments in parallel, across multiple patient subgroups. Formative multi-arm multi-stage trials, such as STAMPEDE accompanied advances in platform trial design (including umbrella and basket trial variants) allowing the recycling of study infrastructure to address new research questions in a continuous fashion [11,12]. Recently, with the addition of techniques like adaptive randomisation, and increased emphasis on the use of routinely collected clinical data, these designs have coalesced into the Randomised Embedded Multifactorial Adaptive Platform (REMAP) approach. Noteworthy examples of this design include the REMAP-CAP and RECOVERY trials, used to great effect in the evaluation of candidate treatments for COVID-19 [13,14].

Despite the continued development of clinical trial design, we are yet to see trials that are fully embedded within Electronic Health Record Systems (EHRS). Both REMAP-CAP and RECOVERY used external randomisation processes and required significant time commitments from clinical research teams for processes such as participant identification and eligibility screening. Therefore, it may be argued that despite clear improvements in efficiency overall, conducting pragmatic trials for CER of the commonest 'everyday' treatments remains logistically and financially impracticable [15].

Consequent to being unable to conduct rapid-cycle comparative effectiveness trials efficiently, clinicians have been left with gaps in the evidence base for many commonly used treatments. Without evidence, uncertainty fills these gaps and clinicians are forced to rely on personal experience and the application of basic scientific knowledge - the lowest rungs of the Evidence Based Medicine (EBM) ladder.

Uncertainty in decision making results in variation in how treatments are applied to patients. Braithwaite et al. have described this as the "60-30-10" problem – where 60% of treatments conform to evidence, 30% are ineffective, and 10% result in harm to patients [16]. At the individual patient or clinician level, variation has been demonstrated in how patients are selected to undergo surgery [17,18], surgical techniques for a given operation [19], in the management of heart failure and diabetic ketoacidosis [20,21], and in the application of treatments like antibiotics and intravenous fluids [22,23].

Prior to the availability of EHRS, it has been technologically infeasible to convert these moments of uncertainty into learning opportunities experimentally, with prospective randomisation. Observational methods have been used to describe treatment heterogeneity, and service evaluations using quality improvement methodology and audit have become well established in healthcare. However, neither quality improvement, nor clinical audit may be reliably used to generate new evidence about treatment effectiveness [24]. They may expose and quantify variance from an established standard, but they cannot reliably discern the impact on patients. By comparing with a research-derived gold standard, the assumption that follows is that variation causes a negative impact on patients. However, this fails to account for scenarios where clinicians personalise care, under the considered acknowledgement that the average treatment effect used in that standard may not directly apply to individuals. Therefore, a more nuanced approach to understanding treatment variation is required.

Observational methods can effectively describe the presence of heterogeneity for a given question but may struggle to reliably quantify effects on outcomes due to issues with bias and confounding [25]. Modern causal inference techniques offer advantages in this respect, through harnessing natural experiments using instrumental variables [26], regression discontinuity designs [27], or difference-in-differences approaches [28], to derive more precise estimates for treatments. Whilst the addition of causal inference methods to observational studies is useful, they require a clear understanding of their assumptions and limitations to be correctly interpreted. In addition, they are methodologically complex and challenging to communicate to clinicians, who may often require a degree of reassurance before adopting new evidence into practice, that may only be met by the presence of prospective randomisation [29].

With increasingly digitally mature health systems, we argue that it is now both possible *and* ethically obligatory to learn from uncertainty in clinical decision making, with the intent of deriving new evidence for the comparative effectiveness of everyday treatments [30]. A thorough understanding of variation requires a multi-pronged approach, using observational methods and aspects of implementation science, but, crucially, it must involve the use of prospective randomisation to confer the required internal validity. To this end, the current RCT design must continue to evolve, circumventing financial barriers and logistical challenges, such that it can be widely applied to CER questions.

We propose that when harnessed within an appropriate methodological, technical, and ethical framework, the variation itself may provide an efficient mechanism for learning and evidence generation. Through observing variation in the application of treatments, estimating the impact of variation on patients, and use of a flexible, digital approach to randomisation, clinicians may harness opportunities to learn from uncertainty, where it is safe and justifiable to do so. We propose to integrate trials of routine treatment effectiveness into everyday clinical care by modifying existing EHRS features. By interceding close to the point of clinical decision making, we

generate an opportunity for the clinician to express their equipoise for a given decision, through adherence to a randomised treatment suggestion.

Central to this design is the idea that each clinical decision is accompanied by a corresponding level of uncertainty as to its relative merits. This 'uncertainty principle' is analogous to the theory of clinical equipoise, first described by Freedman in 1987 [31,32]. Freedman defined clinical equipoise as "honest, professional disagreement among expert clinicians about the preferred treatment" (p144) [32]. Hey et al. expand on this definition, requiring that either or both of two conditions be met for trial participation – that there be "insufficient evidence to warrant a judgment that one intervention in the trial is inferior to the other", or that "some experts favour one intervention over the others, but different experts prefer different interventions for the same patients" (p1) [33].

These principles apply equally to trials integrated into clinical practice. However, rather than requiring consensus from participating clinicians en masse, each may now evaluate and exercise their individual level of uncertainty (personal clinical equipoise) for the study treatment, through the decision of whether to follow a randomised treatment or not.

We propose that identifying the limits and bounds of heterogeneity for a treatment lacking evidence indicates the presence of clinical equipoise within the cohort of clinicians studied. Treatment arms which test the comparative effectiveness of two or more treatment strategies may then be derived, such that they fall within the limits of existing practice variation. Clinicians should, then, feel comfortable enough to suspend their individual treatment preferences (including a lack of any preference) in favour of learning through treatment randomisation. This idea of personal clinical equipoise for individual treatment decisions has been identified as a key step to justifying the conduct of CER within Learning Health Systems (LHS), and is already used in existing trial designs such as preference trials [30,34].

EHRS now provide sufficient structure that key trial processes may be automated [35]. Digitally embedding trial infrastructure is efficient, reducing reliance on manual processes and offering the potential to recycle and repurpose those systems for future research questions at reduced cost. To date, this has predominantly been limited to data collection and eligibility screening. However, essential steps like randomisation and consent remain manual, limiting the scope and scale of learning from clinical practice.

In this special communication we summarise the current state-of-the-art of the clinically integrated randomised trial and highlight recent progress afforded by an informatics-based approach. We describe two barriers to implementation - delivery of randomisation which acknowledges and accommodates clinician treatment preferences, and the requirements for obtaining patient consent to participate in trials of routine treatments. In the final section, we offer our vision of a modern Learning Health System which uses routinely collected EHRS data in a trial pipeline which combines observational analysis of practice variation with rapid-cycle clinically integrated randomised trials to generate new usable knowledge which can be rapidly returned to clinicians to improve care.

1 - Integrated Clinical Trials

Conceptually, harnessing naturally occurring variation in practice within clinical trials lies at the intersection of several research domains. These include: the clinically integrated randomised trial [36] , the Partially Randomised Preference Trial (PRPT) [37], and Point-of-Care Trials (POCT) [38,39]. In this section, we discuss the principles behind each design, highlight CER examples, and describe modern Learning Health Systems (LHS) as a framework for combining these concepts.

1.1 Clinically Integrated Randomised Trials

A clinically integrated randomised trial seeks to replace unevidenced variation in decision making with opportunities for randomisation. The key point emphasised by Vickers and Scardino is that such a trial is so well integrated within the clinical workflow "…that the clinical experience of the patient and doctor is virtually indistinguishable whether or not the patient is randomised" [36]. The authors went on to demonstrate this in a feasibility study which evaluated different surgical approaches for radical prostatectomy [40].

Vickers et al. were able to demonstrate that integrating randomisation into a surgical pathway was feasible and acceptable to patients and clinicians. Their design did not involve significant use of an EHRS, although the importance of obtaining outcome data from routinely recorded clinical data was emphasised. Additionally, the trial design did not incorporate any acknowledgement of clinician preference prior to randomisation, indeed the only method of personalising treatment was for the clinician to deviate from the study protocol after randomisation. Despite this, recorded treatment contamination was low (6/154 and 3/154 participants respectively received a treatment contrary to their randomisation across both study arms). This lack of non-compliance is likely to have resulted from careful selection of the study question, such that clinicians had genuine

equipoise. However, there was significant missing data in both groups regarding treatment received, which makes this difficult to interpret with certainty [40].

With the feasibility of integrating randomised clinical decision making into routine practice established, future work has addressed some of the study's limitations. In particular, the incorporation of treatment preferences, and the use of routinely collected electronic data to improve data capture.

1.2 Partially Randomised Preference Trials

PRPTs seek to explicitly record participant preferences for study treatments. A preference trial aims to minimise bias by only including participants without strong preferences in the randomised study arms [37]. A recent systematic review and meta-analysis provided evidence of improved external validity, inclusivity, and acceptability to participants over classical RCT designs [41]. Additionally, one of the postulated benefits to this design is improved treatment compliance (and therefore internal validity), as participants with strong preferences can receive their treatment of choice, leaving the randomised arms populated by participants with genuine equipoise, and minimising the effects of "resentful demoralization" on outcomes [42].

One example of a PRPT addressing a comparative effectiveness question is the TOIB study. This compared topical versus oral ibuprofen for the treatment of chronic knee pain. A patient preference approach was used in combination with a randomised design as it was expected that patients would have strong motivating factors for choosing a treatment route. The study found no differences in the clinical outcome between randomised and preference groups and concluded that offering either topical or oral ibuprofen had the equivalent effect on knee pain, and where a preference was expressed by a patient it was reasonable to follow it [43].

The principles behind PRPTs may be transferable to clinicians' preferences. This is of relevance to specialties like Critical Care Medicine, where the majority of treatments received as part of

routine care may be determined by the clinician's preference. Here the advantages of a PRPT design hold - critical care clinicians often determine whether individual patients participate in RCTs (where patients lack capacity). If the clinician has a strong belief in the benefits of one of the RCT arms, they may choose not to allow their patient to participate, thus ensuring they are not denied that treatment through randomisation. In this case, a PRPT enables the patient to participate by allowing the clinician to follow their preference. The patient is then able to contribute data to the trial, which is used to understand the effects of preferences on the treatment estimate derived from the randomised cohort in the usual way.

1.3 Point of Care Trials

Point of care trials (POCT) represent the most complete practical examples of integrated clinical trials within the literature. Building on the previous work described, these studies have taken an informatics-based approach, with increased integration of trial infrastructure within EHRS. In the United Kingdom, van Staa and colleagues examined the feasibility of using POCTs to compare statin regimens for treatment of hypercholesterolaemia, and early or delayed antibiotic prescription for exacerbation of chronic obstructive pulmonary disease (COPD) [39]. These studies were both conducted in the primary care setting and revealed specific challenges to using a standard point of care randomisation approach. Both studies used existing EHRS to deliver alerts to clinicians, identifying eligible participants who could then be consented and randomised during the consultation.

Whilst integrating randomisation was technically achievable, both studies struggled to integrate randomised testing into routine care delivery. In these examples, clinicians took on significant responsibilities by participating in the study, namely obtaining informed consent during consultations, in addition to reviewing and actioning the results of randomisation – challenging to complete within the time constraints of a primary care consultation. These examples illustrate that appropriate research question selection and knowledge of clinical workflows are crucial when

considering an integrated clinical trial design. The trial must not place significant additional burdens on care delivery, both for clinicians and patients. Patients clearly found it acceptable to be randomised between equivalent types of statin, a relatively simple question to consider. However, when presenting acutely unwell with respiratory symptoms, a nuanced discussion of randomising between immediate and delayed antibiotic treatment was considerably more challenging.

In contrast, the best current example of a clinically integrated POCT remains that conducted by Louis Fiore and colleagues at the Massachusetts Veterans Epidemiology Research and Information Centre. In 2011, these authors published an ambitious and novel trial design for a POCT comparing insulin administered via a sliding scale with an alternative weight-based regimen [44]. Principles of the clinically integrated trial were again central themes - the trial investigated a commonly used, evidence-light treatment, for which there was equipoise among prescribing clinicians.

The trial design was highly pragmatic - any patient who required an insulin prescription was considered eligible, and screening was integrated into the treatment order process. By modifying the existing electronic treatment order, the study was able to offer clinicians the choice of either treatment arm, plus the option to randomise if there was uncertainty, or no preference. No modifications were made to any of the existing treatment protocols for either study arm, and data collection was confined to routine clinical observations within the EHRS. The authors also took the ambitious decision to incorporate further complexity into the trial design by using adaptive randomisation to optimise allocation of participants to treatment arms showing promise following serial pre-specified interim analyses. Proponents of adaptive randomisation cite the ability to identify successful treatments earlier, thereby reducing the number of participants randomised to ineffective treatment arms [34].

Results of their pilot study were mixed - across nine months, 105 patients were eligible for recruitment, with 61% agreeing to participate, indicating a broad acceptance of the clinical question and the study design. However, clinicians opted for the randomisation option in 28% of eligible

patients, possibly due to unfamiliarity with the study and the POCT design. When approached by a research team member, the proportion agreeing to randomisation increased to 80%. One of the advantages of building a complex trial system within the EHRS is that small iterative changes may be introduced to optimise design. To this end, the authors have attempted to increase participation by enforcing an "opt-in or opt-out" randomisation checkpoint before the treatment order can be accessed.

Whilst Fiore et al.'s trial design is commendable; it serves to illustrate the complex nature of designing fully integrated clinical trials within EHRS and highlights several limitations. The study design continues to rely heavily upon research teams for establishing patient consent. In their introduction, the authors state that optimally integrating trials into clinical care would "include recruitment and randomization of study subjects at their POC by their usual healthcare provider" (p184). We would suggest that this is not feasible, either by clinicians (as demonstrated by van Staa et al.), or by research teams, due to the costs involved in scaling these studies. We explore this issue in the next section. Furthermore, we believe that this design does not take full advantage of the opportunity to collect data on clinicians' preferences for treatments. As already described, treatment preferences can be the result of conscious and appropriate treatment personalisation using expert judgement. In these cases, clinician preferences should not only be followed, but learned from. We believe incorporating a PRPT design, allowing the discernment of preference and selection effects, will add value to the already efficient study design demonstrated by Fiore et al.

Overall, the POCT examples described represent a major advance in the field of integrated clinical trials by demonstrating the feasibility of delivering randomisation electronically to clinicians close to the point of decision making. However, they have also highlighted areas for improvement and optimisation, through incorporation of preference trial concepts and through seeking alternative methods of obtaining consent to participate in CER trials.

1.4 Learning Health Systems

Over a decade on from the original description, Learning Health Systems (LHS) could be said to now represent the current stage of evolution for the clinically integrated trial. LHS offer a framework within which CER and integrated trial designs may be connected. As defined by Foley et al., a LHS is one in which "…outcomes and experience are continually improved by applying science, informatics, incentives and culture to generate and use knowledge in the delivery of care " (p5) [45]. This definition expounds the key principle of a LHS – that routinely collected clinical data is used to create knowledge, which is then returned to clinical practice and re-evaluated, a system which Friedman et al. described as engendering a "virtuous cycle of health improvement" (p45) [46]. Specifically, LHS acknowledge that generating successful cycles of evaluation and new knowledge creation is also reliant upon fostering an appropriate culture within healthcare institutions.

Integrated clinical trials represent one method of knowledge generation within LHS - indeed, because they incorporate randomisation, the evidence generated may be of greater validity. However, implementing randomisation effectively remains a barrier to the widespread conduct of integrated trials, and examples of systems routinely using these methods remain scarce. One successful example is New York Langone Health, where integrated randomisation has been used to test the effectiveness of existing and new quality improvement projects [47]. The authors have separately proposed using the A/B testing approaches normally seen in informatics to iteratively evaluate the development of interventions such as computerised clinical decision support tools [48].

1.5 Summary

Thus far, automating elements of clinical trial infrastructure such as the identification of eligible participants and the extraction of routinely collected clinical data has proven feasible. However, it is evident that delivering randomisation at the point of care and finding the optimal way to deliver proportionate informed consent for integrated trials both remain clear barriers to progress. Since the original description of the integrated clinical trial in 2009, progress has been made in developing the research methods underpinning point of care randomisation and its implementation within LHS. Despite this, there remain few trials demonstrating the feasibility of delivering integrated randomisation within EHRS, for the evaluation of comparative effectiveness questions at scale. Additionally, there are few examples of LHS which are actively generating new evidence for treatment effectiveness and returning it to clinicians to improve future practice. In the next section we summarise current arguments around alternative consent mechanisms for routine CER within LHS.

2 - Ethics and Consent

One of the key questions which must be addressed before integrating randomisation into clinical care, is how patients should consent to participate in these studies. This is a complex issue, which remains under debate in the literature. Obtaining consent manually generates significant logistical complexity and financial cost within a clinical trial. Conversely, alternative approaches which circumvent direct consent, such as waiver of consent, may lack proportionality and be unsuitable for the research question under consideration.

Within the authors' domains of critical care and cardiology, a spectrum of consent methods may be applicable, depending on the research question, the patient, and the setting. The potential options are illustrated in **Figure 1**.
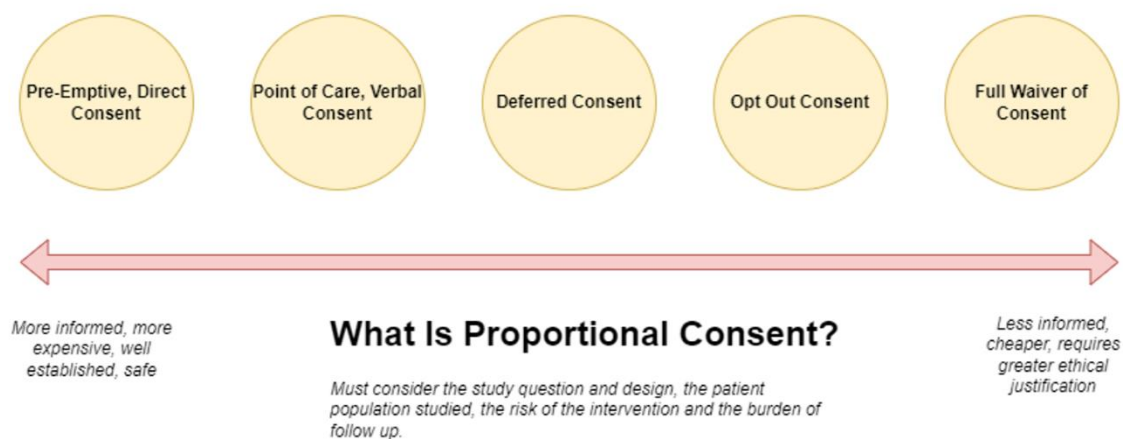

Figure 1: The spectrum of consent methods for comparative effectiveness research studies

For patients undergoing elective surgery, who may be predicted to require critical care postoperatively, obtaining study consent may be done pre-emptively, prior to the operation, whilst they retain capacity. This method of consent is logistically demanding, requiring multiple patient contacts, provision of written information, and follow up for signing of written consent. However, this process is thought to convey the most rigorous imparting of informed consent. Whilst potentially suitable for patients expecting to come to critical care, this method excludes patients who present emergently and incapacitated. Often, the lack of available research staff out of hours precludes recruiting patients admitted at night, or over weekends, potentially resulting in selection bias.

At the opposite end of the scale, where it is not possible to provide consent directly, or where the process of obtaining consent precludes the conduct of the trial, a waiver of consent may be granted. Critical care trials frequently operate under a deferred consent model, where consent is waived to allow recruitment, until the earliest possible opportunity following the participant regaining capacity.

For CER questions, the current method of obtaining consent manually, at the point of meeting eligibility criteria would be prohibitively disruptive to patients and the delivery of care. Obtaining written consent for multiple treatment questions would not be practical. As we have seen in the example studies from van Staa and colleagues, clinicians and patients will be wary of any processes which complicate care delivery, no matter how relevant the research question. However, obtaining verbal consent at the point of care, where the patient retains capacity may be a viable alternative. In the United States, Simon et al. have described two point-of-care trials which use a verbal consent statement, delivered by the clinician, and approved by an ethics committee to consent the patient in the outpatient clinic setting for two CER questions [49]. Whilst this streamlines the consent process by making it analogous to a standard clinician-patient treatment discussion, it may not fully address concerns about whether this represents fully informed patient consent. Rather, this

represents an example of a *proportional* consent approach. The patient is not incapacitated, and therefore a waiver of consent would seem inappropriate, but a classical direct consent approach precludes conducting the trial integrated within clinical care. This method permits additional layers of safety through providing participants with a mechanism to opt-out of the study, should they wish to do so at a later stage.

Whilst a verbal consent approach offers clear advantages, it may still remain too burdensome. For clinicians in the UK, this approach would currently require additional research training, which must be conducted prior to recruiting patients into a trial [50]. This places an additional burden on clinicians engaging with integrated clinical trials. There is, however, an argument that this approach to consent is not necessary for routine CER treatment questions. Faden et al. have argued that it may be ethically justifiable not to obtain express informed consent from participants for research questions under select circumstances [30,51,52]. Where a treatment lacks good evidence but continues to be routinely administered, research comparing strategies which fall within the bounds of normal variation do not require the same degree of explicit informed consent as novel therapeutic agents, or repurposed treatments. Indeed, these treatment questions fall within a grey zone between those which clearly represent clinical audit or quality improvement questions (where current use is compared to an existing standard), and novel treatment investigations, which present more substantial risk to patients. Making this distinction between research and clinical practice Kass et al. argue that the classical definition of research as the evaluation of an "untested clinical intervention", together with the starting expectation that these interventions should have a reasonable prospect for benefit which outweighs the prospect of risk, should *not* apply to treatments already in common use [53].

As Kass and colleagues describe, a strong empirical assumption about what constitutes research is that there is an inherently higher risk to the patient than standard clinical practice. Studying treatments within the limits of existing variation addresses this concern in part because the risk to the patient of participating may be no greater than receiving standard care. A caveat to this is

where clinicians want to vary treatment in response to a particular individual circumstances. In this case, following a treatment protocol within a study without question may result in the patient receiving suboptimal care through study participation. As such, when considering the concept of an integrated trial it is necessary to consider situations where clinicians will lack equipoise with the study question and deviate from the trial protocol. Permitting this to happen maintains safety but may reduce trial efficiency through the introduction of non-compliance with randomisation.

Under the select circumstances described it may be justifiable to adopt a consent model which is less disruptive to the successful conduct of an integrated clinical trial. One option is to offer an opt-out consent approach, similar to that which is already used for the conduct of secondary research using routinely collected clinical data [54]. We envisage a scenario in which patients attending hospital, at first on an elective basis, are provided with information regarding the routine conduct of integrated clinical trials and are provided mechanisms to opt-out where they would prefer. This could take an informatics-driven approach, as increasingly patients interact with hospitals remotely through the EHRS. In many cases, they are already asked to give preferences for being contacted by the hospital. It would be a simple undertaking to ask the patient, upon registering with the EHRS, for their preferences surrounding trial enrolment. Patients would then be able to consider multiple trials that are currently running and judge their relative acceptability accordingly.

For patients happy to participate this would then move the burden of obtaining consent away from the point of become eligible, such that there is no disruption to clinical care. Research questions using this method would require careful screening and justification to both trial management groups (including patient representatives) and ethics committees. If sufficient public engagement with an opt out process can be demonstrated, it may also become acceptable to extend this practice to patients admitted under emergency conditions.

Work in evaluating the potential acceptability of this approach continues and Faden et al. have put

forward the basis for a suitable regulatory framework to use when considering the appropriateness of a research question. This framework includes that interventions being evaluated should be low risk, that the trial should not adversely affect patient outcomes, and that clinical freedom to provide optimal care is preserved [52]. **Table 1** sets out the seven moral obligations described by Faden et al., together with how our proposed design addresses the same. These points were further developed by Fiore et al. in 2016. Here, the authors proposed precise criteria for judging the appropriateness of a treatment effectiveness question for integration into clinical practice using point-of-care randomisation [55]. These points are summarised in **Table 2**.

Whether alternative consent models such as the opt out method described are acceptable under the terms of reference proposed in Table 1 and 2 remains the subject of ongoing research. In 2018, Morain et al. evaluated stakeholder views on three consent models – opt in, opt out, and "general approval" for observational and randomised CER questions. The general approval model was the most light touch, consisting of passive information about study participation (e.g. leaflets, posters), without routine explanation of the studies by clinicians, and no specific opportunity to opt out of participation. 67% of participants found this model acceptable for observational studies. However, this fell to 11% when randomised studies were considered. Further work must address where stakeholders feel comfortable on the spectrum between the classical opt in approach and the general approval model used [56].

In 2015, the UK Health Research Authority commissioned a detailed public dialogue exercise exploring issues around consent for CER studies, finding broad support for the idea of "zero consent ", under specific criteria. These included the use of anonymised outcome data, application to low-risk areas of research, assurance that the interventions studied are not intrusive or invasive, and a requirement for a "genuine lack of knowledge about the best treatment" [57].

To summarise - ensuring the feasibility of integrated clinical trials requires alternative approaches to informed consent. The debate around whether the investigation of routinely varying treatments which lack evidence constitutes research in the formal sense, or rather a variant of quality

improvement continues. It is the authors' position that CER under the criteria described do represent formal research undertakings, but the current burden of governance and model for obtaining consent is likely disproportionate for questions which adhere to the frameworks described. As the existing literature suggests "cautious acceptability" from stakeholders, to advance this field we now need to have practical testing of integrated clinical trials and the acceptability of alternative consent models to patients, families, clinicians and the wider public.

Seven Moral Obligations for Learning Health Systems	Our Proposed System
1. Respect the rights and dignity of patients	Acknowledge that where care is not evidence-based, use consent models proportionate to the research question.
2. Respect the clinical judgements of clinicians	Offer flexible randomisation where clinicians share equipoise for the treatment question.
3. Provide optimal care to each patient	Clinicians retain the ability to follow their treatment preference at all times.
4. Avoid burdensome non-clinical risks to patients	No research questions that require additional data collection or follow up requirements.
5. Reduce health inequalities among populations	Highlight populations where clinicians lack equipoise and prioritise further study. Efficient trials enable rapid recycling across subgroups. Lightweight consent models open up research participation to low take up populations.
6. Foster learning from clinical care and clinical information	Generate learning from every clinical decision which is reliable and rapidly translatable to clinicians.
7. Improve quality and value of clinical care	Minimise the use of unevidenced and ineffective treatments.

Table 1: Addressing the seven moral obligations for Learning Health Systems

Criteria for CER Questions Using Clinically Integrated Trial Designs
1. *Treatment in common use*
2. *Acknowledged uncertainty regarding treatment effectiveness*
3. *Strong clinician desire to explore comparative effectiveness*
4. *Well described toxicity profile*
5. *Study design proposed results in minimal disruption to normal clinical workflow*
6. *Electronic health record sufficiently configurable to study the required workflows*
7. *Electronic health record has sufficient "back-end" infrastructure to support the data collection required for the study*
8. *All electronic mechanisms determining care are monitored and verified by human experts*

Table 2: Criteria proposed by Fiore et al. for evaluation of candidate comparative effectiveness research (CER) questions for integrated clinical trials

3 - Clinically Integrated Randomised Trials in a Learning Health System

In this section, we present our vision of how a clinically integrated randomised trial, embedded within an EHRS may be undertaken, and highlight the work we have done thus far to make this a reality. Our LHS builds on each of the trial designs described in section one, and addresses the barriers highlighted in section two.

3.1   System Overview

Our LHS has two potential entry points. First, clinical teams are engaged with the research design and encouraged to produce candidate research questions for consideration in the trial platform. Clinician engagement is essential for integrated trials. If clinical teams do not feel engaged with the study question, or feel that it is not relevant, then it is likely that compliance with randomisation at the point of care will be low. Candidate questions are then screened by the research team against the existing evidence base. If there is evidence for the correct treatment, a clinical audit or quality improvement approach may be preferable. The question should also be examined against the criteria in Table 2. An alternative, data-driven approach to defining the study question may also be used. This should then be presented back to clinical teams to ensure that what is observed represents a genuine problem in clinical practice.

If the proposed treatment question lacks good evidence, the next step is to assess the current level of variation in practice at the individual clinician and patient level. This approach should use routinely collected EHRS data, in tandem with an observational study design which is appropriate to addressing two questions: 1) what is the current level of treatment heterogeneity present in the study population, and 2) what is the impact of this heterogeneity on a clinically relevant outcome

measure? Using an EHRS-based approach enables a parallel assessment of whether data quality would support a future integrated trial, and ensures the data collected is relevant to the local population of clinicians and patients. Furthermore, by delineating the boundaries of existing variation in practice, we ensure that a future randomised trial operates within them and does not test "novel" treatment strategies. If a causal link between existing variation in practice is identified, whether the observational study alone provides sufficient evidence to recommend changes to clinical practice should be evaluated. However, in isolation, it is unlikely that this approach will yield inferences sufficiently reliable to stimulate clinicians to change practice.

Whilst heterogeneity may be identified using EHRS data, understanding the reasons underpinning it may be more challenging. Whilst observational data may be interrogated to identify specific subgroups of patients with shared characteristics that may prompt certain behaviours, the best way to understand local practice variation is to amalgamate this approach with a qualitative approach. Rapid qualitative studies, including interviews and ethnography may add key information to inform the design of a future prospective trial, particularly using an integrated approach, where a detailed understanding of clinical workflows is essential to success [58].

Having identified the limits of existing variation in practice, and linked these to an important clinical outcome, the next step is to use this information to evaluate different strategies in a prospective, randomised point of care trial. The trial should be both integrated into the clinical workflow and embedded within the EHR. This allows easy replacement of the treatment decision, with randomisation, through acknowledgement of an electronic prompt received by the clinician, close to the point of decision making. The trial should be highly pragmatic in nature, seeking to replace a single clinical decision, whilst leaving the rest of the clinical workflow intact.

Finally, having accrued sufficient data to allow interpretation, the point of care randomisation system may be modified to reflect this new evidence. As such, the system allows clinicians to randomise a decision within a study, where treatment lacks evidence, and present the clinician with timely decision support where evidence exists.

3.2   Worked Example

We sought to test the feasibility of this study design and identified a commonly encountered clinical question on the critical care unit, lacking evidence in the literature, as an example to test our LHS – *does a liberal approach to magnesium supplementation reduce the risk of developing abnormal heart rhythms such as atrial fibrillation in critical care patients?*

We undertook an EHRS-based observational study of magnesium supplementation practices at our institution. Using multilevel modelling we were able to identify and quantify variation in magnesium supplementation practices attributable to individual clinicians (in this case, the critical care nurse, the primary decision maker for magnesium supplementation at our institution). By constructing a natural experiment, using the nurse's preference for magnesium administration as an instrumental variable, we were able to estimate the impact of the variation on our chosen clinical outcome measure of atrial fibrillation [59].

Using the results of our observational work we designed a prospective feasibility study to evaluate two methods of flexible, electronic, point of care randomisation. The study continues the use of our candidate question of magnesium supplementation and allows critical care nurses to replace their usual supplementation decision with a randomised suggestion to either liberal or restrictive supplementation strategies. In keeping with the principles of an integrated trial, the design is highly pragmatic in nature. Decisions around treatment administration and monitoring remain at the discretion of the clinical team but are monitored through the EHRS. The study is also embedded

within the EHRS, with automated patient screening, application of inclusion and exclusion criteria, integrated point of care randomisation using modified clinical decision support architecture and recording of routinely collected electronic data pertinent to the trial outcomes.

Notably, our feasibility study compares two designs of electronic point of care randomisation prompt. The first design follows the principles of a preference trial, following the example of Fiore et al. [44]. Here, the bedside critical care nurse is presented with trial information close to the point of making the decision to supplement magnesium. They are then asked to select whether they have a strong preference for or against supplementing magnesium, or whether they have no preference. In the case of a strong preference, the nurse follows their treatment decision and the patient supplies data to the observational arm of the study. If the nurse has sufficient uncertainty, they may follow the randomised suggestion and contribute data to the experimental study arm.

We compare this preference design with a more simplified 'nudge' design. This presents the nurse with the same trial information, alongside a randomised, non-mandated suggestion to administer magnesium, or not. If the nudge proves sufficiently powerful, then this becomes an instrumental variable which can be used to derive an estimate of treatment effect once sufficient study numbers have accrued. Further detail on our study design may be found in the trial protocol [60], or on ClinicalTrials.gov, NCT 05149820.

3.3 Advances in Methodology

Our approach builds on that described by Fiore et al. and presented in section 1.3. Similarities include the integrated nature of the trial within clinical workflows, a highly pragmatic approach to study design with no changes to existing treatment protocols, use of routinely collected electronic data for all clinical outcomes, and use of an interruptive electronic alert to prompt clinicians to randomise treatment.

We differ in four ways. Firstly, we modify existing clinical decision support infrastructure to facilitate randomisation at the point of clinical decision, rather than the system of electronic medication orders used by Fiore and colleagues. This allows us to target clinical decision makers relevant to our treatment question (bedside critical care nurses). This approach will allow integrated trials to be conducted among non-prescribing decision makers in the future.

Second, we design the system to be responsive to changes in patient state. It is normal practice for critically unwell patients to have their serum magnesium measured, and a decision about whether to supplement or not daily. By linking the point of care randomisation alert to the daily serum magnesium result, we gather data for each magnesium administration opportunity. This differs from the single randomisation point in Fiore et al's study, where there was one insulin treatment per patient.

Third, like Fiore et al., we use a preference design approach where the clinician is invited to highlight a preference via the alert, or express equipoise through selection of the randomised treatment. We will aim to use preference arms as a parallel observational study, in the format of a PRPT design, to eventually ascertain preference and selection effect which may contribute additional knowledge from the trial in addition to findings from the randomised treatment arms. We also test a design of prompt which uses the behavioural science principle of nudging to achieve a similar effect with lower alert burden.

Finally, we distance participant consent away from the point of randomisation, using a pre-emptive consent approach for patients undergoing elective surgery, expecting critical care admission. To evaluate patient attitudes towards changing this strategy to a more lightweight consent model, such an opt out consent framework, we are collecting participant interview data in a parallel qualitative evaluation in our study population.

Conclusion

At present, routine clinical practice contains multiple evidence gaps and clinicians experience uncertainty in how to apply treatments optimally. These uncertainties must be navigated daily, and patients experience unwarranted variation as a result. Given the large number of treatment questions relating to routine care, and the desire to pursue ever more personalised treatment, it will not be possible to address these questions with ever larger, or more comprehensive RCTs due to prohibitive costs.

A LHS approach, using the efficiencies of the EHRS offers a broad solution, but integrating clinical trials within this structure remains an elusive goal. To address this problem, we have described a system which uses point of care randomisation combined with either a preference trial design or nudge randomisation approach.

By replacing the obligation to randomise with a flexible opportunity, we integrate trials safely and learn from clinical experience. Through embedding remaining trial infrastructure within EHRS, such that the entire study workflow is delivered during the clinical interaction, these trials become efficient and rapid cycling. Flexible point of care randomisation also increases recruitment opportunities - each time the clinician encounters the decision (day or night) they have the option to randomise.

Despite the existing barriers to delivering integrated clinical trials, we believe that this research pipeline represents an exciting advance in the field of LHS. If successful, it has the potential to lead to a healthcare system which can truly embrace Friedman's vision for a "virtuous cycle of learning", to the benefit of both patients and clinicians.

Author Contributions

MGW, SKH and FWA conceived the idea for this commentary. MGW prepared the initial draft of the manuscript, and all authors were involved in contributing major edits. All authors read and approved the final manuscript prior to submission.

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