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ANALYSIS

Low risk pragmatic trials do not always require participants' informed consent

Clinical trial regulations should remove unnecessary obstacles for the conduct of pragmatic trials assessing the comparative effectiveness of medicines posing no or minimal risk to participants, say **Rafael Dal-Ré and colleagues**

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Key messages

- Randomised controlled trials do not always inform daily clinical practice because of limited generalisability
- Low risk pragmatic randomised controlled trials can assess comparative effectiveness of interventions with no or only minimal incremental risk
- Obtaining written informed consent for these trials can hamper recruitment and reduce the generalisability of results
- Council for International Organizations of Medical Sciences guidelines state that written informed consent can be waived if the research would be impractical if consent was required, has important social value, poses no more than minimal risk to participants, and is approved by a research ethics committee
- EU clinical trial regulations should be revised to allow the waiver or modification of informed consent in low risk pragmatic trials

Real world comparative effectiveness research is an important component of evidence-based medicine. Observational data can be collected in routine clinical practice but often have poor procedural quality and are prone to confounding, leading to overestimation of treatment effects.[1] Randomised controlled trials (RCTs) are the gold standard for determining a causal effect of interventions, but they can have a critical limitation: the results may not be applicable to other settings.[2] Two factors that prevent generalisability of RCT results are strict participant selection criteria and the informed consent process—both can lead to a patient group that bears little resemblance to the population the treatment will be used in. Moreover, RCTs are susceptible to the Hawthorne effect, whereby participants may change their behaviour when they are aware of taking part in research.

RCTs may create an artificial world—for example, 79% of RCTs assessing interventions for chronic conditions exclude patients with concomitant chronic conditions.[3] Thus, RCTs do not always provide useful evidence to inform patients and clinicians in their daily practice. A quarter of patients routinely treated with oral anticoagulants, for example, were excluded from the RCTs that led to guidelines, and these exclusion criteria affected the risk of major bleeding.[4]

Pragmatic RCTs

Pragmatic RCTs aim to provide evidence of immediate relevance to the decisions of patients, healthcare professionals, and policy makers by assessing interventions as prescribed, managed, and used in normal clinical practice. This removes many of the features that can make RCTs artificial. Only two characteristics of pragmatic RCTs interfere with the normal patient-physician relationship: randomisation and the need to seek written

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informed consent from each participant. When the perceived benefit:risk comparative ratios of two interventions is uncertain, randomisation is the fairest way of allocating treatment and is the best way to handle unknown confounders.

Low risk pragmatic RCTs

Low risk pragmatic RCTs pose no or minimal incremental risk compared with usual clinical care[5] and are typically head to head comparisons of medicines that are routinely prescribed according to their marketing authorisations. There are several approaches to conducting low risk pragmatic RCTs of medicines. Two of them—registry based trials[6] and using electronic health records (thus embedding the trial within usual clinical practice in a point-of-care RCT[7])—could facilitate implementation, recruitment, and follow-up.

The critical point in low risk pragmatic trials that do not add non-standard activities or data collection is that randomisation of individual participants poses no additional risk to them, as both treatments would be considered appropriate with similar perceived benefit:risk ratios. That the choice will be made at random is the most important thing that potential participants should know before consenting.

To establish equipoise in the perceived benefit:risk ratios at the design stage of the protocol, investigators should consider the efficacy and safety profiles and seek the views of patients. Contraindications and interactions that preclude patients from participating in the trial should be defined as exclusion criteria in the protocol. For patients who satisfy the criteria, as in normal routine, doctors will discuss the advantages and disadvantages of the medicines. After the patient consents to treatment, randomisation takes place and the patient is allocated to receive one of the two treatments; the physician tells the patient about specific adverse reactions or interactions to be avoided. At this stage the patient should agree to be treated with the medicine that has been assigned. As in usual care, this does not interfere with the normal shared decision making process between physicians and patients.

To ensure that the trial fully resembles routine care, the number of procedures, tests, and periodicity of visits should be virtually the same as in normal clinical practice, without extra baseline or outcome assessments. Participants should have no more risks or burden than patients in usual clinical practice. But this is not enough for a trial to qualify as pragmatic—36% of 89 published randomised trials of medicines that were labelled as pragmatic clearly deviated from normal clinical practice and had a low degree of pragmatism.[8] The PRECIS-2 tool can help investigators ensure a high degree of pragmatism in the design, conduct, and analysis of the trial.[8]

Although low risk pragmatic RCTs are close to the ideal design for primary care health research (and other settings), they can be challenging to conduct. In addition to problems with recruiting clinicians as investigators,[7 9] the administrative ethics approval of the trial's protocol,[7] and reporting of adverse events,[7 10] an important hurdle for the recruitment of patients is related to the informed consent process (table 1).

Informed consent

Many clinical trial regulations require that any patient participating in a pragmatic RCT must provide written informed consent. Obtaining this is a disruption of the normal patient-physician encounter,[11] as it entails the use of a participant's information sheet and a conversation about the details of the trial. The consent process, however, does not prevent a consistently poor understanding of the information provided.[12] Moreover, these materials do not always perform well against current standards for shared decision making.[13]

The requirement for consent could also lead to the recruitment of a selected group of patients,[14] and make the trial impracticable—that is, it will not be able to provide generalisable results on the research question. For example, recruiters may expect that a potential participant will say no, or is already anxious, so they do not ask. Or they may not attempt to recruit potential participants in whom the consent process is more burdensome (such as those with low literacy or poor hearing). On the other hand, patients may consider the consent process intrusive or suggestive of excessive risk and therefore decide not to participate. Thus, the participants may inadvertently end up being a selected subgroup of the whole potential target population. In the worst scenario, the trial is terminated early.[7 11] We should look for alternatives to the standard written informed consent for low risk pragmatic RCTs.[22 23]

Proposed solutions

Ethics

Bioethicists and investigators support alternatives to standard written informed consent. These include advance written consent documented in the electronic health record to be subsequently confirmed by the participant's verbal consent at the time of enrolment[15] or verbal consent after the participant is briefly informed about the main features of the trial (notably, randomisation) in a clinical encounter.[16] Another possible approach is "general notification," whereby potential participants are aware that healthcare and research are simultaneously provided and seeking informed consent for a specific trial is considered ethically unnecessary.[17 18] A risk based approach to informed consent has been proposed, in which low risk pragmatic RCTs of medicines prescribed according to their approved marketing authorisations are considered to provide no more than minimal incremental risk to that of standard care.[19]

In surveys on hypothetical low risk pragmatic RCTs, most of the public preferred written informed consent to verbal consent or general notification, although substantial minorities of up to 40%[20 21] endorsed the alternative option over the standard written consent.

Current evidence around modifications to the consent process or format shows little or no effect on recruitment compared with standard written consent.[24] Electronic informed consent[25] is starting to be used[26] but could lead to a non-representative group of participants. Should we then consider including participants in low risk pragmatic RCTs without seeking informed consent? Is this approach ethically acceptable?

Clinical investigators agree that, when dealing with competent patients, all trials that randomise individual participants should comply with the ethical principle of respect for persons and allow patients to accept or reject participation. But if a waiver of informed consent was the only way a trial of high social value could be done, would these same investigators change their minds? Surveys conducted in the US have shown that both the public[27] and patients[28] who endorse written or verbal consent in low risk pragmatic RCTs change their minds if this would make the trial impractical.

Regulations

Canadian[29] and US[30] regulations support modifying or waiving the need for participants' informed consent in human research

with high social value if specific requirements are fulfilled (table 2). This is not true, however, for the EU regulations[32] due to be fully implemented in 2019 or those of Argentina,[33] Australia,[34] and South Africa.[35] These regulations are hampering the conduct of important low risk pragmatic RCTs that could provide evidence for comparative effectiveness (benefiting future patients) and comparative efficiency (benefiting public health budgets).

The EU regulations,[32] which refer to low risk pragmatic RCTs as "low intervention" trials (box 1), do allow for simplified consent in cluster trials (box 2).

Box 1: Definition of low intervention clinical trials* according to EU regulations[32]

A low intervention clinical trial is one that fulfils all the following conditions:

- The investigational medicinal products, excluding placebos, are authorised
- According to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation or their use is evidence based and supported by published scientific evidence on their safety and efficacy in any of the member states concerned
- Additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the participants compared with normal clinical practice in any member state concerned

*Low risk pragmatic randomised controlled trials randomising at participant level

Box 2: Low risk pragmatic randomised controlled trials: respect for persons and social benefit[31]

In its first guideline, the Council for International Organizations of Medical Sciences (CIOMS) juxtaposes social value and respect for persons (or autonomy), which is applied through seeking explicit informed consent from prospective participants or (legally) authorised third parties acting on their behalf, when appropriate. Social value is what justifies research and needs to be supplemented with proper respect for persons.

In healthcare research, respect for persons is accomplished in two ways—by striving for the most effective treatment possible and by seeking informed consent when necessary. Recent discussions on learning healthcare systems[36] have brought this out clearly, noting that clinical practice is increasingly intertwined with research.[37] In such a system, gathering beneficial knowledge for society is seen as an intrinsic feature that both patients and healthcare professionals participate in.[18]

Low risk pragmatic RCTs are perhaps the best possible example of what these systems aim for: to learn from ongoing activities affecting real world patients under real world conditions, thereby gaining best evidence for treatment choice and for directing care, and resources, to those who will most likely benefit. Respect for persons is here shown in the continuing endeavour to improve the evidence base and reduce the risk of suboptimal treatment. The standard paradigm in research ethics—where a sharp distinction is made between research and care—will only hamper important steps forward and needs to be challenged.

Many low risk pragmatic trials assessing comparative effectiveness of commercially available medicines could fulfil the three provisions of the Council for International Organizations of Medical Sciences (CIOMS) ethical guidelines (table 2): impracticality of the trial without waiving consent, important social value, and posing no more than minimal risk. Firstly, investigators should include all eligible individuals to ensure generalisability of results. Trials with expected small treatment effects or small differences in treatment effect sizes will need to recruit hundreds or thousands of participants; the targeted recruitment could be at risk without waiving informed consent.

Secondly, these RCTs are of little interest to industrial sponsors and manyneed to be supported with public funding. Having head to head valid comparisons of commonly prescribed medicines is crucial to making evidence informed and value for money decisions in the NHS.[38] The social value of pragmatic RCTs, such as those in table 3, should not be a judgment made by researchers alone but should be supported by patient involvement at the design stage[39] and when reviewed by the relevant research ethics committee (including patient members).

Thirdly, testing medicines according to their marketing authorisation and without non-standard activities or data collection poses no more than minimal risk, with no incremental risk or burden than prescription in routine care. Many low risk pragmatic RCTs of medicines with clinical equipoise, where patients are not expected to prefer one (as assessed through the meaningful involvement of patients in the trial design process)[39] could fulfil these three provisions and could be deemed ethical even if informed consent is waived.

The number of low risk pragmatic trials evaluating the comparative effectiveness of medicines remains very low,[40] despite their high social value. The hurdles preventing such studies must be overcome.

Actions to improve the current situation

Scientific methods

For a consent waiver to be appropriate, the trial must be as close to clinical practice as possible. In their trial protocols, investigators must show a high degree of trial pragmatism[8]—for example, using the PRECIS-2 tool[41]—when asking research ethics committee for a modification or waiver of a participant's informed consent. This is important because a low risk trial with low degree of pragmatism cannot provide generalisable results and therefore will not have important social value.

Regulations

The US Food and Drugs Administration has stated that it will not object to a waiver of consent for minimal risk clinical investigations granted by institutional review boards.[42] Canadian regulations also permit alteration or waiver of informed consent.[29] US and Canadian regulations state that investigators should consider debriefing participants after they have finished taking part. This is possible for most low risk pragmatic RCTs, or at least those in chronic diseases or conditions. Alternatively, general notification of the simultaneous conduct of care and research could be made public through letters, posters, and brochures (at the centres where healthcare is provided).

The EU (and other jurisdictions) should consider introducing some flexibility around the requirements of consent for low risk pragmatic RCTs. There is arguably a moral need to make use of essential scientific information to inform clinical decision making. Flexibility around consent would also be in line with the spirit and provisions of the EU General Data Protection Regulation (GDPR)[43] that recently came into force. GDPR states the legitimate grounds that data could be used for scientific research—the research objective itself legitimates the use of personal health data, with the condition that participants' rights and interests are protected with adequate safeguards on data processing, which will include technical and organisational measures such as data minimisation and pseudonymisation. From the perspective of protecting personal data, the EU standards rely on the way researchers and institutions manage the data, not on a dogmatic approach to consent of the participant. Data minimisation is fulfilled in low risk pragmatic trials as the data collected are those obtained in usual clinical practice, and pseudonymisation is standard in all types of clinical trial.

Ethical guidelines

The World Medical Association should debate and, hopefully, include provisions for modification or waiver of informed

consent for research such as low risk pragmatic RCTs in the Declaration of Helsinki. This would align the positions of the two most influential ethical guidelines for health related research in their approach to this type of RCT—an important step in implementing trials aimed to answer questions raised in usual clinical practice.

Conclusions

Over-regulation of research comparing alternative standard treatments presents a formidable challenge—by making that research harder to do, it will likely prolong clinical uncertainties.[44] Evaluation of routinely used medicinesin pragmatic RCTs is a moral imperative,[45] but unfortunately it occurs too little owing to several barriers, one of which is seeking the participant's written informed consent. Professional and patients' associations, research ethics committees, regulators, and, eventually, members of parliaments of interested jurisdictions, must work towards issuing recommendations and making legally possible what is ethically acceptable: modification or waiver of informed consent in certain types of low risk pragmatic RCTs.

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Tables

Table 1| Examples of the challenges of pragmatic RCTs that required individual patient consent

Trial	Summary	Sample size	Recruitment	Consent related barriers to trial participation
Mosis et al[11]	Patients in a Dutch primary care electronic health record system were randomly allocated to receive diclofenac or celecoxib for osteoarthritis to compare gastrointestinal tolerability. Both drugs were licensed, marketed, and reimbursed for the treatment of osteoarthritis. All patients >18 years old who were diagnosed with osteoarthritis, needed a non-steroidal anti-inflammatory drug for osteoarthritis, and were not treated in the past 3 months were eligible for the study	170 patients identified	Of the eligible patients, only 20 were randomly assigned to a drug. In 30 cases the patient was not recruited because the doctor was too busy to start the recruitment procedure. Another 55 patients received treatment in the practice but from a healthcare professional not involved in the trial	Doctors experienced patient recruitment as a time consuming disruption of the normal work flow, especially because of the need to obtain informed consent
van Staa et al[7]	Point-of-care trial in the UK including patients aged ≥40 years with a medical history of chronic obstructive pulmonary disease (COPD) who, in the opinion of their GP, had an acute exacerbation of COPD with an increase of non-purulent sputum volume, who did not require immediate referral to specialist care for treatment of COPD exacerbation and consented to participation. Patients were randomly assigned to receive immediate (prophylactic), deferred, or non-use of antibiotics	150 patients	31 patients were recruited for the eLung trial (two trials were included in the publication)	Information disclosure in the trial was much more detailed and onerous than that outside the trial. Consent would be too difficult to obtain in a consultation

Table 2| Modifications and waivers of informed consent in Canadian and US regulations and in Council for International Organizations of Medical Sciences (CIOMS) guidelines

Canadian regulations[29]	*US regulations*[30]	*CIOMS guidelines**[31]
The research ethics board may approve research that involves an alteration† to the requirements for consent . . . if is satisfied, and documents, that all the following apply: the research involves no more than minimal risk to the participants the alteration to consent requirements is unlikely to adversely affect the welfare of participants it is impossible or impracticable to carry out the research and to address the research question properly, given the research design, if the prior consent of participants is required in the case of a proposed alteration, the precise nature and extent of any proposed alteration is defined and the plan to provide a debriefing (if any), which may also offer participants the possibility of refusing consent and/or withdrawing data and/or human biological materials	An institutional review board [ethics committee] may approve a consent procedure that does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the board finds and documents that: the research involves no more than minimal risk‡ to the participants the waiver or alteration will not adversely affect the rights and welfare of the participants the research could not practicably be carried out without the waiver or alteration, and whenever appropriate, the participants will be provided with additional pertinent information after participation	A research ethics committee may approve a modification or waiver of informed consent to research if: the research would not be feasible or practicable to carry out without the waiver or modification the research has important social value, and the research poses no more than minimal risks to participants

* CIOMS guidelines were prepared in collaboration with the World Health Organization. †Alterations to consent requirements may include providing prospective participants with only partial disclosure about the purpose of the study, deceiving prospective participants entirely about the purpose of the study, and not informing participants that they (or their data or biological materials) are part of a study.[29] ‡Minimal risk: the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or in routine physical or psychological examinations or tests. In evaluating risks and benefits, the institutional review board should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of treatments that participants would receive even if not participating in the research).[30]

Table 3| Currently active or not yet recruiting pragmatic RCTs of medicines of important social value that could be eased with the modification or waiver of written informed consent

Trial name	Reference	Disease	Objective	No of participants
ADAPTABLE	NCT02697916	Atherosclerotic cardiovascular disease	Effectiveness of two different doses of aspirin in patients at high risk of ischaemic events	20 000
RELIANCE	HSRP20162204	Chronic obstructive pulmonary disease	Roflumilast *v* azithromycin to prevent exacerbations	3200
TRANSFORM-HF	NCT03296813	Heart failure	Torasemide *v* furosemide in hospital inpatients	6000
PRIORITIZE	NCT02786537 HSRP20162126	Hepatitis C	Comparison of oral treatments (ledipasvir with sofosbuvir *v* ombitasvir with paritaprevir and ritonavir *v* elbasvir with grazoprevir *v* dasabuvir)	1676
MOTS	NCT02764320	Migraine	Determining the optimal treatment strategy for chronic migraine patients with medication overuse	1280
PRAG-MS	NCT03345940 HSRP20164132	Multiple sclerosis	Fingolimod *v* dimethylfumarate in patient overall disease experience in relapsing remitting multiple sclerosis	1360

All are open label, parallel group, multicentre trials. All are self labelled as pragmatic or belong to the Patient-Centered Outcomes Research Institute's funding programme for trials to evaluate patient centred outcomes (https://www.pcori.org/). To qualify as low risk pragmatic RCTs, all trials should show a high degree of pragmatism and that they pose no more than minimal risk or no more than minimal incremental risk to that of standard care.