Low-risk pragmatic trials with medicines and the need for participant’s informed consent

Standfirst: Jurisdictions should remove, where appropriate, unnecessary obstacles for its conduct

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There is great interest in gathering real-world evidence on the comparative effectiveness of health interventions. Because of limited generalizability, randomized controlled trials do not always inform daily clinical practice.

Pragmatic randomized controlled trials (pRCTs) can assess comparative effectiveness of interventions with no or only minimal incremental risk. Among others, obtaining written informed consent can be an important hurdle to some of those low-risk trials, may hamper recruitment rendering the trial impractical: the results will have no generalizability.

While the EU clinical trials regulations require participants’ written informed consent also in low-risk participant-level pRCTs with medicines, a modification or waiver of informed consent is accepted in Canada and the US. So do the CIOMS ethical guidelines, as long as the trial is impractical without waving consent, has important social value, poses no more than minimal risk to participants, and it is approved by a research ethics committee.

Clinical trials regulations of a number of jurisdictions should be revised to accept the possibility of the waiver or modification of informed consent in low-risk participant-level pRCTs as per the CIOMS guidelines provisions. This would facilitate the conduct of low-risk pRCTs of critical public health importance.

Key words: real-world evidence; pragmatic trials; informed consent; CIOMS guidelines; clinical trials regulations; waiver of informed consent
Clinical research to support evidence-based clinical practice

Real-world comparative effectiveness research is an important component of evidence-based medicine that supports clinical practice. Such data could be obtained from retrospective observational studies to double-blind randomized controlled trials (RCTs). One efficient way to obtain this type of data is by reviewing and analyzing data collected in routine clinical practice. However, this type of observational data often has poor procedural quality, is prone to confounding, thereby often overestimating treatment effects. RCTs are the gold standard to determine a causal effect of interventions. Still, they can have a critical limitation: generalization of the results to other settings. Two of the factors that prevent generalizability of RCTs 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, it can lead to the Hawthorne effect: participants may change their behavior once aware of taking part in a research. RCTs may create an artificial world: for instance, 79% of RCTs assessing interventions for chronic conditions excluded patients with concomitant chronic conditions. The final result is that RCTs do not always provide useful evidence to inform patients and clinicians in their daily practice. For example, for one of the most widely used treatments (oral anticoagulation), a quarter of patients routinely treated with these drugs had been excluded from the RCTs that led to guidelines to use these drugs, and these exclusion criteria affected the risk of major bleeding.

Pragmatic RCTs

The clinical usefulness of RCTs would be dramatically improved when pragmatic RCTs (pRCTs) were extensively performed to assess comparative effectiveness of available interventions. pRCTs aim to provide evidence of immediate relevance to the decisions of patients, healthcare professionals and policymakers by assessing interventions as prescribed, managed and used as
in normal clinical practice. In pRCTs many of the features that make RCTs rather artificial
disappear, as they are not distanced from usual clinical practice. Only two characteristics are
left that interfere with the normal patient-physician relationship: randomization and the need
to seek written informed consent from each participant. Where the perceived benefit/risk
comparative ratios of, for instance, the two medicines involved is uncertain, randomization is
the fairest way of allocating treatment and is the best way to handle unknown confounders.

Low-risk pragmatic RCTs

Low-risk pRCTs pose no or only minimal incremental risk compared with usual clinical care⁵,
and typically involve head-to-head comparisons of medicines that are routinely prescribed
according to their marketing authorizations. There are several approaches to conducting low-
risk pRCTs with medicines. Two of them, registry-based RCTs⁶ and the use of electronic health
records (thus embedding the RCT within usual clinical practice in ‘point-of-care’ RCT⁷) could
facilitate implementation, recruitment and follow-up.

The critical point in low-risk pRCTs that do not add nonstandard activities or data collection, is
that randomization poses no additional risk to participants, since both of the treatments would
be considered an appropriate choice with similar perceived benefit/risk ratios. That the choice
will be made at random is the single most important trial feature that one might think should
be known by potential participants before consenting.

It should be emphasized that the comparative assessment of the perceived benefit/risk ratios
of medicines of interest should consider both efficacy and safety profiles to establish equipoise
of the medicines at the design stage of the protocol and should be done together with patient
representatives. Also, contraindications and interactions related to the drugs to be studied
precluding patients from participating in the pRCT should be defined as exclusion criteria in the
protocol. With the patients satisfying the criteria it will be discussed as in normal routine what
the advantages and disadvantages are of yes or no treatment with the medicines, for instance, the use or not of a statin when two statins will be compared in the pRCT. After the consent of the patient to be treated, randomization will take place and depending on the allocation of one of the two medicines the physician will inform the patient about specific adverse drug reactions or interactions to be avoided related to the selected medicine. At this stage the patient should agree to be treated with the medicine that has been assigned. This approach, as in usual care, does not interfere with the normal shared decision process between physicians and patients.

To ensure 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: there should be no extra baseline and outcome assessments. Hence, there are no extra risks and burden to participants as in usual clinical practice. But this is not enough for a trial to qualify as a pRCT: 36% of RCTs with medicines self-labelled as pragmatic clearly deviate from normal clinical practice and were conducted with low degree of pragmatism\(^8\). Accordingly, investigators should ensure a high degree of pragmatism in the design, conduct and analysis of the trial\(^8\).

Although low-risk pRCTs are close to the ideal design for primary-care health research (as well as in other settings), the challenge of their conduct can be more substantial than their low-risk warrants.

**Current problems to the conduct of pragmatic RCTs to inform clinical practice: informed consent**

Many current clinical trials regulations require that any patient participating in this type of RCT must provide his/her written informed consent. However, in addition to a number of problems such as 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). Obtaining the standard written informed consent is a disruption of the normal patient-physician encounter since it entails the use of a participant’s information sheet and a conversation on the trial’s specifics. However, the informed consent process does not prevent a consistently poor understanding of the information provided. Moreover, these materials do not always perform well against current standards for shared decision making. The requirement for consent could also lead to the recruitment of a selected group of patients and make the trial impracticable i.e., will not answer the research question by rendering limited or no generalizable results. The informed consent process may hamper the inclusion of patients on either side: recruiters may expect that a potential participant will say no, or is already anxious, so do not ask; or they may not attempt to recruit potential participants in whom the consent process is more burdensome to administer (e.g. those with low literacy, those with poor hearing or other disadvantaged groups). From the patient’s side, the consent process may be considered intrusive, or suggestive of excessive risk and cause rejection to participate. Inadvertently patients who accept participation end up being a selected subgroup of the whole potential target population. In the worst-case scenario, the trial has to be early terminated.

Proposed solutions to the written informed consent hurdle: the ethics and the regulations

The ethics

The scenario described above has prompted bioethicists and investigators to support alternatives to standard written informed consent. For example, advance written consent documented in the electronic health record to be subsequently confirmed by participant’s verbal consent at the time of enrolment or, even, a verbal consent after the participant is briefly informed about the main features (notably, randomization) of the trial within a clinical encounter. But also, to providing no explicit trial information at all, when potential
participants are aware that health care and research are simultaneously provided (the so-called ‘general notification’ approach), where seeking informed consent is considered to be ethically unnecessary\textsuperscript{17,18}. Since different types of pRCTs could pose different risks to participants, a risk-based approach to informed consent has been proposed in which low-risk pRCTs with medicines prescribed according to their already approved marketing authorizations are considered to provide no more than minimal incremental risk to that of standard care\textsuperscript{19}. In surveys on hypothetical low-risk participant-level pRCTs with medicines a majority of the public preferred written informed consent to verbal consent or general notification; however, substantial minorities of up to 40\%\textsuperscript{20,21} endorsed the alternative option over the standard written consent.

We should look for alternatives to the standard written informed consent for low-risk pRCTs\textsuperscript{22,23}. Current evidence around modifications to the consent process or format has found them to generally have little or no effect on recruitment compared to standard written consent\textsuperscript{24}. Electronic informed consent\textsuperscript{25} is starting to be used\textsuperscript{26}, but could lead to a non-representative group of participants. Should we then consider including participants in low-risk pRCTs with medicines without seeking informed consent? Is this approach ethically acceptable?

Clinical investigators agree that, when dealing with competent patients, all types of participant-level RCTs should comply with the ethical principle of respect for persons by giving patients the opportunity to accept or reject their participation in the trial. However, if a waiver of informed consent is the only way a trial of high social value can be done, would these same investigators change their minds? Surveys conducted in the US have shown that both the public\textsuperscript{27} and patients\textsuperscript{28} endorsing written or verbal consent in low-risk participant-level pRCTs change their minds if this would make the trial impractical.
The regulations: current scenario

The Canadian\textsuperscript{79} and US\textsuperscript{80} regulations support the conduct of high social value human research with the modification or waiver of participants’ informed consent if specific requirements are fulfilled (Table 2). This is, however, ignored by the clinical trials regulations of the EU\textsuperscript{32} - due to be fully implemented in 2019- and that of countries such as Argentina\textsuperscript{33}, Australia\textsuperscript{34} and South Africa\textsuperscript{35}. However, the EU regulation\textsuperscript{32}, where low-risk pRCTs are called ‘low-intervention’ trials (Table 3), does allow for simplified consent in cluster trials. Similarly, could simplified consent or its waiver be acceptable for low-risk pRCTs? (Table 4).

The regulations: looking forward

Many low-risk pRCTs assessing comparative effectiveness of commercially available medicines could fulfill the three provisions of the recently issued CIOMS (WHO) guidelines (Table 2): impracticality of the trial without waving consent, important social value and posing no more than minimal risk. First, investigators should include all eligible individuals to ensure generalizability of results: trials with expected small treatment effects or anticipated small difference in treatments effect sizes will need to recruit hundreds or thousands of participants; the targeted recruitment could be at risk without waiving informed consent. Second, these RCTs are of little interest to industrial sponsors and almost all need to be supported with public funding. Having head-to-head valid comparisons of commonly prescribed medications is crucial to making evidence-informed and value for money decisions within the national health systems\textsuperscript{38}; the social value of such research such as that shown in Table 5, should not be a judgement made by researchers alone but rather should be supported by patient involvement both at trial design\textsuperscript{39} and when reviewed by the relevant research ethics committee and the patients’ representatives within its membership. And third, testing the medicines according to their marketing authorization and without nonstandard activities or data collection, poses no more than minimal risk, with no incremental risk or burden than prescription in routine care.
Many low-risk pRCTs with medicines, with clinical equipoise, where patients are not expected to have preference for one medicine or the other -as assessed through the meaningful involvement of patients in the trial design process\textsuperscript{39}, could fulfill these three provisions and could be deemed ethical even if informed consent is waived.

The number of low-risk pRCTs evaluating the comparative effectiveness of medicines remains very low\textsuperscript{40}, despite their high social value. It is necessary to overcome the hurdles preventing such studies. As discussed above, one of these hurdles is that many low-risk pRCTs would be impractical without waiving of written informed consent. In the EU\textsuperscript{32}, and a number of other jurisdictions, however, research ethics committees will be reluctant to approve any waiver of written informed consent in trials with medicines as this will be in breach of the clinical trials regulations. Therefore, these regulations are hampering the conduct of important low-risk pRCTs that could provide evidence for comparative effectiveness (benefiting future patients) and comparative efficiency (benefiting public health budgets).

\textbf{Actions to improve the current situation: methodology, regulations and ethical guidelines}

\textbf{The scientific methodology}

For a consent waiver to be appropriate, the overall design approach of a trial must be highly pragmatic: the modus operandi in routine clinical practice is a key component in the justification for the waiver. In their trial protocols, investigators should demonstrate a high degree of trial pragmatism\textsuperscript{4} -for instance, with the use of the PRECIS-2 tool\textsuperscript{41}- when requesting the relevant research ethics committee that the trial could be conducted with a modification or waiver of participant’s informed consent. This is crucial since a low-risk pRCT with low degree of pragmatism cannot yield generalizable results and, hence, will not be of important social value.
The regulations

The US FDA has recently stated that it will not object to a waiver of consent for minimal risk clinical investigations granted by institutional review boards. Current Canadian regulation permits alteration or waiver of informed consent. The regulations of the US and Canada state that debriefing of participants, once their participation has been concluded, should be considered. This is possible for most low-risk participant-level pRCTs, at least those of chronic diseases or conditions. As an alternative to debriefing, general notification of the simultaneous conduct of care and research could be made public through letters, posters and brochures (at the centers where health care is provided).

The EU (and other jurisdictions) should reflect on introducing some flexibility around the requirements of consent for low-risk pRCTs with medicines. This would arguably be a moral need to make use of essential scientific information to inform clinical decision-making. This flexibility around consent would seem to be also in line with the spirit and provisions of the EU General Data Protection Regulation (GDPR) that recently came into force. GDPR states that there are legitimate grounds that data could be used for scientific (e.g. medical) research; it is the research objective itself that legitimates the use of personal health data, with the condition that participant’s rights and interests are protected with adequate safeguards on data processing which will include technical and organizational measures such as data minimization and pseudonymization. Therefore, from the protection of personal data perspective, the EU standards rely on the way researchers and institutions manage the data, not on a dogmatic approach to consent of the participant. In low-risk pRCTs data minimization is fulfilled since the data to be collected is that of usual clinical practice and pseudonymization 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 pRCTs in the Declaration of Helsinki. This would align the position of the two most influential health-related research ethical guidelines in their approach to this type of RCT - an important step to facilitate the implementation of trials aimed to answer questions raised in usual clinical practice.

Conclusion

Over-regulation of research comparing alternative standard treatments presents a formidable challenge and by making that research harder to do, will likely prolong clinical uncertainties. We consider that evaluation of routinely used medicines in pRCTs is a moral imperative, but unfortunately occurs too little due to several hurdles: seeking participant’s written informed consent is a critical one. The time has come for professional and patients’ associations, research ethics committees, regulators and, eventually, members of parliaments of interested jurisdictions, to work towards issuing recommendations and making legally possible what is ethically acceptable: modification or waiver of informed consent in certain types of low-risk pRCTs.
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Authors’ contributions

R Dal-Ré wrote the first draft of the manuscript. All authors provided comments and edits throughout the drafting process for important intellectual content. All authors approved the final version of the manuscript and are accountable for all aspects included in it. R Dal-Ré is the guarantor of the article.

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Declaration of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that have neither financial nor non-financial interests that may be relevant to the submitted work except for James that reports grants and personal fees from AstraZeneca, Bayer, Boston Sc, Abbott; and grants from Jansen and Ted Med Co, outside the submitted work. Mentz reports grants and personal fees from Amgen, Novartis, Merck and Luitpold; grants from AstraZeneca, GSK and Bayer; and personal fees from Boehringer Ingelheim during the conduct of the study. Perucca reports personal fees from UCB Pharma, Eisai Inc, GW
Pharma, Mylan, Livanova, Sun Pharma, Sanofi, Takeda, Medichem, other from Wiley and Elsevier, outside the submitted work.

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Secretariat on Responsible Conduct of Research, Ottawa, Canada.


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

<table>
<thead>
<tr>
<th>Summary</th>
<th>Sample size</th>
<th>Actual recruitment</th>
<th>Investigator comment on consent-related barriers to trial participation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients within a Dutch primary care electronic health record system were randomised in a randomised database study to compare gastrointestinal tolerability in persons treated with diclofenac and celecoxib for osteoarthritis. Both drugs were licensed, marketed, and reimbursed for the treatment of osteoarthritis. All patients &gt;18 years older who were diagnosed with osteoarthritis, needed a NSAID for osteoarthritis, and were not treated in the last 3 months were eligible for the study.</td>
<td>170 eligible patients were identified. Of the eligible patients, only 20 were randomised. In 30 cases the patient was not recruited because the doctor said he or she was too busy to start the recruitment procedure. Another 55 patients did receive treatment in the practice but from a healthcare provider not involved in (or therefore trained for) the trial.</td>
<td>Patient recruitment was experienced as a time-consuming disruption of the normal work flow, especially because of the need to obtain informed consent.</td>
<td>Mosis et al11</td>
<td></td>
</tr>
</tbody>
</table>
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 general practitioner, 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 randomised between immediate (prophylactic) versus deferred or non-use of antibiotics.

| Patients | 150 patients through primary care. | 31 patients were recruited. | Information disclosure in trial much more detailed and onerous compared with that outside trial. Consent would be too difficult to obtain within a consultation | eLung
van Staa et al7 |
Table 2.- Modifications and waivers of informed consent in Canada and US regulations and in CIOMS guidelines

<table>
<thead>
<tr>
<th>Canada Regulation²⁹</th>
<th>US Regulation³⁰</th>
<th>CIOMS (WHO) guidelines (a)³¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>The research ethics board (b) may approve research that involves an alteration (c) to the requirements for consent set out in (…) if is satisfied, and documents, that all the following apply:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. the research involves no more than minimal risk to the participants;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. the alteration to consent requirements is unlikely to adversely affect the welfare of participants;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. 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;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. in the case of a proposed alteration, the precise nature and extent of any proposed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>An institutional review board (b) may approve a consent procedure which 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 IRB finds and documents that:</td>
<td></td>
</tr>
<tr>
<td>1. the research involves no more than minimal risk (d) to the subjects;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. the waiver or alteration will not adversely affect the rights and welfare of the subjects;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. the research could not practicably be carried out without the waiver or alteration; and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. whenever appropriate, the subjects will be provided with additional pertinent information after participation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A research ethics committee may approve a modification or waiver of informed consent to research if:</td>
<td></td>
</tr>
<tr>
<td>1. the research would not be feasible or practicable to carry out without the waiver or modification;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. the research has important social value; and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. the research poses no more than minimal risks to participants.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
alteration is defined; and

5. 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 (…)

(a) CIOMS guidelines were prepared in collaboration with the World Health Organization, Geneva, Switzerland.
(b) In the US, institutional review boards, and in Canada, research ethics boards, are equivalent to research ethics committees in the EU.
(c) 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 involved in a study.
(d) 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 during the performance of 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 therapies subjects would receive even if not participating in the research).
Table 3: Low-intervention clinical trial\(^a\) definition as per the EU clinical trials regulation\(^{32}\).

Low-intervention clinical trial, is a clinical trial which fulfils all of the following conditions:
(a) the investigational medicinal products, excluding placebos, are authorized;
(b) according to the protocol of the clinical trial,
   (i) the investigational medicinal products are used in accordance with the terms of the marketing authorization; or
   (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned

\(^a\)Or low-risk pragmatic randomized controlled trial.
Table 4.- Low-risk pragmatic randomized controlled trials and learning healthcare system: respect for persons (autonomy) and social benefit and the CIOMS guidelines\textsuperscript{31}

In its first guideline, CIOMS notably juxtaposes social value and respect for persons (or autonomy), which is applied through seeking explicit informed consent from prospective participants -or (legally) authorized third parties acting on behalf of these individuals, when appropriate. This is not just to contrast them; rather, social value is what justifies research. Although a necessary condition for ethical acceptability, social value needs to be supplemented with proper respect for persons. In healthcare-related research, respect for person is accomplished in two ways 1) by striving for the most effective treatment possible, and 2) by seeking informed consent when necessary. Recent discussions on, for instance, learning healthcare systems\textsuperscript{36} has brought this out clearly, noting that today, clinical practice is increasingly intertwined with research\textsuperscript{37}. In such a system, gathering of beneficial knowledge for society is seen as an intrinsic feature that both patients and healthcare professionals participate in\textsuperscript{18}. Low-risk pRCTs is perhaps the best possible example of what such 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 thereby 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 for suboptimal treatment. The standard paradigm in research ethics – where a sharp distinction is made between research and care – will only hamper such important steps forward, and therefore needs to be challenged.
Table 5.- Examples of currently active or not yet recruiting pragmatic RCTs with medicines of important social value that could be eased with the modification or waiver of written informed consent. All of them are open label, parallel-group, multicenter trials.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Objective</th>
<th>Number of participants</th>
<th>Acronym</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic Cardiovascular Disease</td>
<td>Effectiveness of two different doses of aspirin in patients at high risk for ischemic events</td>
<td>20000</td>
<td>ADAPTABLE</td>
<td>NCT02697916</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>Roflumilast vs azithromycin to prevent COPD exacerbations</td>
<td>3200</td>
<td>RELIANCE</td>
<td>HSRP20162204</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Torsemide vs furosemide in hospitalized patients</td>
<td>6000</td>
<td>TRANSFORM-HF</td>
<td>NCT03296813</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Comparison of oral treatments (sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir and dasabuvir)</td>
<td>1676</td>
<td>PRIORITIZE</td>
<td>NCT02786537 HSRP20162126</td>
</tr>
<tr>
<td>Migraine</td>
<td>Determining the optimal treatment strategy for chronic migraine patients with medication overuse</td>
<td>1280</td>
<td>MOTS</td>
<td>NCT02764320</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Fingolimod vs dimethyl-fumarate in patient overall disease experience in relapsing remitting multiple sclerosis</td>
<td>1360</td>
<td>PRAG-MS</td>
<td>NCT03345940 HSRP20164132</td>
</tr>
</tbody>
</table>

All these RCTs are self-labelled as ‘pragmatic’ or belong to PCORi’s (https://www.pcori.org/) Pragmatic clinical studies and large simple trials to evaluate patient-centered outcomes. To qualify as low-risk pragmatic RCTs, all these trials should demonstrate both 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.