What are Pragmatic Clinical Trials?
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1 Introduction
There has been a recent resurgence in the use of the term ‘pragmatic clinical trial’, but what are they?
This document summarises the current literature, proposed legislative changes (i.e., the EU Clinical Trials Regulation) and guidelines on pragmatic clinical trials (PCTs).

2 The Life of a Drug After Clinical Trials
During the development of a new drug, the primary focus is on assessing whether it’s safe (i.e., the benefit to the patient outweighs the impact of the side effects) and whether it works (Ref - Explanatory Trial/Study). In order to answer these questions, it’s important to remove as many variables as possible, which means testing on patients who have as few as possible medical conditions, other than the one being investigated, and who are taking a minimal number of other drugs (i.e., concomitant medications).

**Definition: Explanatory Trial/Study**
A study whose main objective is to ascertain some preliminary facts or to familiarize researchers with a problem or technology, often without a clear or precise hypothesis; or, sometimes, to screen several hypotheses at once in a preliminary fashion.


However, the drug will be used on ‘real people’, which usually means we have a multitude of medical conditions (that seem to grow exponentially as we grow older) and we are taking a variety of drugs in order to combat these conditions and the side effects of the drugs. There are the over the counter (OTC) drugs that we use when needed, such as painkillers, anti-histamines, hang-over cures etc.
The drug wasn’t tested in all these ‘real world’ scenarios, to do so would be impractical.

2.1 The Need for ‘Real World Evidence’
There is a significant knowledge gap regarding the benefit of these drugs once they have been approved.

We need to know whether these drugs work as well in the real world as they did in clinical trials and whether there are new side effects/ adverse reactions that were not seen previously. We also need to know whether the new drug is better/ more beneficial than drugs already on the market, whether it’s used properly by the prescribing doctors
and the patients (i.e. as per the instructions provided in the drug label). Obviously, I’m over-simplifying things here, but you get the message.

So how do we get this information/ fill this knowledge gap?

We assess the use of these drugs in situations identical to, or close to, routine clinical practice. These assessments can either be interventional (e.g., we dictate which patients receive which drug in a research protocol, but the drug is still used according to it’s authorized purpose) or non-interventional (i.e., the patient is already receiving the drug and we collect information on how it’s being used, how well it’s working, and what side effects/ adverse reactions the patient experiences).

### 2.2 Generating Real World Evidence through Interventional Clinical Trials

These types of trials are not the same as the ‘pre-approval’ clinical trials because the drug is being used according to it’s approved purpose. The ‘intervention’ is by virtue of dictating which of the approved drugs the patient will receive. This is what we mean when we refer to ‘Pragmatic Clinical Trials’ (Ref – Definition: Pragmatic Trial/ Study).

**Definition: Pragmatic Trial/ Study**

A study (including randomized clinical trials) whose aim is to determine the effects of an intervention under the usual conditions in which it will be applied. By contrast with an EXPLANATORY STUDY, the focus is on guiding decision e.g., about healthcare.


### 2.3 Generating Real World Evidence through Non-Interventional Research

If you want to know how effective a drug is and what side effects/ adverse reactions are being experienced in the patient population receiving your drug during routine clinical practice, then you need to collect this data from a large number of these patients. This is one of the main purposes of non-interventional studies (also referred to as ‘Observational Studies’ and ‘Registries’).

**Definition: Non-Interventional Trial (EU Directive 2001/20/EC)**

Non-Interventional Study or Non-Interventional Trial: a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied.
Figure 1 – The Continuum of Product Development and Evidence Generation

This figure illustrates where Pragmatic Clinical Trials (PCTs) fit in the continuum of product development and evidence generation.

3 WHAT ARE PRAGMATIC CLINICAL TRIALS?

Pragmatic clinical trials (PCTs) are randomized trials that seek to compare the effectiveness of two or more interventions in real-world settings. Generally, PCTs are closely integrated with clinical practice, incorporate outcomes that are relevant to patients and other relevant stakeholders, include a broad range of clinical settings, and have minimal exclusion criteria so that the patients reflect those receiving care outside of the trial. These trials seek clinically applicable evidence about the relative advantages and disadvantages of interventions to inform the decisions made by clinicians, patients, and others (Ref: New Definition for a PCT?). Recently, given pressures to improve healthcare quality and interest in transforming healthcare institutions into learning
healthcare systems, PCTs have received increased emphasis and support (Whicher et al., 2015).

New Definition for a PCT?
Califf et al., (2015) propose three key attributes of PCTs:

1) An intent to inform decision-makers (patients, clinicians, administrators, and policy-makers), as opposed to elucidating a biological or social mechanism;

2) An intent to enroll a population relevant to the decision in practice and representative of the patients or populations and clinical settings for whom the decision is relevant; and

3) Either an intent to
   a) streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial, or
   b) measure a broad range of outcomes

Given these attributes, a common-sense definition for a PCT would thus be as follows:

“Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level” (Califf et al., 2015)

3.1 Explanatory (RCTs) vs Pragmatic Clinical Trials

The explanatory trial is the best design to explore if and how an intervention works, and the whole experiment is designed in order to control for all known biases and confounders, so that the intervention’s effect is maximized. Usually the intervention under examination is compared with a placebo or with another active treatment (Patsopoulos, 2011).

The pragmatic trial, on the other hand, is designed to test interventions in the full spectrum of everyday clinical settings in order to maximize applicability and generalizability. The research question under investigation is whether an intervention actually works in real life. The intervention is evaluated against other ones (established or not) of the same or different class, in routine practice settings. Pragmatic trials measure a wide spectrum of outcomes, mostly patient-centered, whereas explanatory trials focus on measurable symptoms or markers (clinical or biological) (Patsopoulos, 2011).

Generally, the explanatory trials focus towards homogeneity, so that the errors and biases will influence the results as little as possible, whereas pragmatic trials are a race towards maximal heterogeneity in all aspects, eg, patients, treatments, clinical settings, etc. In order to overcome the inherited heterogeneity, which leads to dilution of the
effect, pragmatic trials must be large enough (to increase power to detect small effects) and simple in their design. Simple trials are easier to plan, perform, and follow up (Patsopoulos, 2011).

Policy makers have an active interest in pragmatic trials, since these are designed to answer the question most relevant to a decision maker’s agenda: comparative effectiveness of interventions in the routine practice. Along with the implementation of cost-effectiveness analyses, pragmatic trials can inform policy makers and health care providers of a treatment’s cost in real-life situations. Thus, decision makers are active partners in the design of the pragmatic trials (Patsopoulos, 2011).

4 What is the Purpose of Pragmatic Clinical Trials?

Pragmatic clinical trials seek to determine the effectiveness of an intervention in a real-world setting to inform clinical decision-making (Roland and Torgerson, 1998).

Researchers designing pragmatic trials take particular care to ensure that the study population is as similar as possible to the population on which the intervention is meant to be used (external validity), reflecting the normal range of diversity in disease severity, comorbidities, age, sex, and social and ethnic groups seen in everyday clinical practice. Pragmatic trials also ensure that the sorts of interventions tested can be plausibly rolled out in clinical practice and that the outcomes used to assess effectiveness are valid and easily understood by a range of users, including clinicians, patients, policy makers, and health commissioners (Williams et al., 2015).

Pragmatic clinical trial patients may also be used to test “strategies” or treatment policies rather than one specific drug at a time. For example, the BLISTER (Bullous Pemphigoid Steroids and Tetracyclines Study) randomized controlled trial tests the policy of starting treatment for bullous pemphigoid patients with either doxycycline or prednisolone (Chalmers et al., 2015). The policy evaluates the trade-off between the short-term smaller benefit for blister control, as might be anticipated for doxycycline, and the long-term safety concerns that may disadvantage patients randomized to prednisolone. It does not matter whether the dose of prednisolone is altered during the study as would normally occur in clinical practice, nor does it matter if some of the patients initially randomized to the strategy of starting with doxycycline are switched subsequently to prednisolone—what matters is a comparison of the two strategies to which the participants were originally randomized. Cost-effectiveness analysis is usually a key component of pragmatic trials to enable care providers to make informed decisions on value for money (Thomas et al., 2006) (Williams et al., 2015).

4.1 Purpose of Pragmatic Clinical Trials

- Pragmatic clinical trials seek to answer important questions that are applicable to everyday clinical practice.
• The design of pragmatic trials aims to test an intervention in a study environment that is closer to real life in terms of study population, intervention, comparator, and outcomes.

• Pragmatic trials must still adhere to the stringent trial methods for minimizing selection, performance, information, attrition, selective outcome reporting, and publication bias.

• Pragmatic trials must be prospectively registered and reported fully according to the pragmatic trials extension of the CONSORT statement.

• The PRECIS tool is one method for assessing where on the pragmatic–explanatory continuum a trial resides and which aspects are more pragmatic or explanatory.

• More pragmatic trials should be considered in dermatology so that they better inform patient care.

4.2 Limitations

• Pragmatic clinical trials can cost more than explanatory trials, and may require a more complex study design.

• The majority of clinical trials are neither entirely pragmatic nor entirely explanatory—they are part of a continuum.

• Pragmatic trials are not suitable for early trials that seek to explore whether a new experimental intervention shows any biological effect.

(Williams et al., 2015)
5 Exploring the Ethical and Regulatory Issues in Pragmatic Clinical Trials

Physicians and health-care systems who are motivated to provide the highest-quality care naturally seek to reduce the uncertainty surrounding decision-making processes affecting health and health-care delivery. Ideally, each of their recommendations and actions should be based in high-quality evidence and reflect an informed understanding of the optimal balance of benefit and risk for their patients. Although the gold standard for such decisions has been (and remains) data from randomized clinical trials, there is increasing recognition that results from experiments done in specialized, highly controlled research settings may not be uniformly generalizable to “real-world” practice (Califf et al., 2015).

In other words, there is a gap between efficacy and effectiveness that analyses of existing data can bridge. Experience suggests that the best way to accelerate improvement in clinical outcomes is to conduct efficient clinical trials that enjoy broad support from patients and providers and then implement those findings within quality health systems. This approach—itself fundamental to the learning health system concept—has yielded a number of notable successes. For example, it has likely contributed to a significant reduction in the rate of death from myocardial infarction at US hospitals, increased life expectancy in cystic fibrosis patients by more than a decade, and led to enormous improvements in survival for children with cancer. One shared aspect of these systematic efforts to improve care and medical outcomes is a transformation of traditional roles, in which patients and their families become the strongest advocates for research and seek out physicians, care teams, and practices.
with a commitment to research and learning in practice. In such settings, patients may band together to volunteer relevant data in order to enhance understanding of the medical and social issues they face and accelerate development of new diagnostic strategies and therapies (Califf et al., 2015). Nevertheless, while pragmatic clinical trials can bridge clinical practice and research, they may also raise difficult ethical and regulatory challenges (Califf et al., 2015).

Because medical therapies that are known to be effective usually have relatively modest effects, establishing whether one such therapy is better than another necessitates the use of an appropriate research design. Two core elements tend to be critical: (1) sample sizes large enough to detect those effects; and (2) the use of randomization to control for potential biases. Broad recognition of the importance of these factors has led to major efforts both within the United States and abroad. In 2008, the US Food and Drug Administration (FDA) created the Sentinel Initiative to analyze medical data from over 100 million Americans in order to illuminate issues related to the safety of medical products following their approval for marketing. This system now incorporates medical insurance claims data from over 150 million Americans, as well as a growing body of data gathered from EHRs. Sentinel projects are exempt from federal requirements to obtain individual informed consent and review by institutional review boards (IRBs) (Califf et al., 2015).

5.1 Ethical and Regulatory Challenges Specific to PCTs

These include the following*:

1) The role of gatekeepers (Whicher et al., 2015)
2) Harmonization and streamlining of IRBs oversight (O'Rourke et al., 2015)
3) Distinctions between research and quality-improvement activities (Finkelstein et al., 2015)
5) Identifying direct and indirect subjects (Smalley et al., 2015)
6) Determining what constitutes “no more than minimal risk” research (Lantos et al., 2015)
7) The use of waiver or modification of informed consent (McKinney et al., 2015)
8) Engaging vulnerable subjects (Welch et al., 2015)
9) Investigations involving the use of FDA-regulated products (Anderson et al., 2015)
10) Privacy (McGraw et al., 2015)

* Source: Califf et al., 2015
6 Privacy and Confidentiality in Pragmatic Clinical Trials

With pragmatic clinical trials, an opportunity exists to answer important questions about the relative risks, burdens, and benefits of therapeutic interventions. However, concerns about protecting the privacy of this information are significant and must be balanced with the imperative to learn from the data gathered in routine clinical practice. Traditional privacy protections for research uses of identifiable information rely disproportionately on informed consent or authorizations, based on a presumption that this is necessary to fulfill ethical principles of respect for persons. But frequently, the ideal of informed consent is not realized in its implementation. Moreover, the principle of respect for persons—which encompasses their interests in health information privacy—can be honored through other mechanisms. Data anonymization also plays a role in protecting privacy but is not suitable for all research, particularly pragmatic clinical trials (McGraw et al., 2015).

7 Exploring PCTs in the Context of the EU Clinical Trials Regulation

Note – The EU Clinical Trials Regulation (Regulation EU/2014/536), is not currently in force. The following information is for information and preparatory purposes only.

7.1 Introducing the Broader Concept of ‘Clinical Study’

The EU Clinical Trial Regulation (Regulation EU/2014/536 – EU – EU CTR) introduces a broader concept of ‘clinical study’ of which the clinical trial is a category and introduces the concept of the low-intervention clinical trial, otherwise know as a pragmatic clinical trial (Figure 2). Each category is defined on the basis of specific criteria (see below). This approach takes due account of international guidelines, and is in line with the Union law governing medicinal products, which builds on the dichotomy of ‘clinical trial’ and ‘non-interventional study’ (as per Recital 3 of Regulation EU/2014/536).
7.1.1 EU CTR DEFINITIONS

‘Clinical study’ means any investigation in relation to humans intended:

a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

b) to identify any adverse reactions to one or more medicinal products; or

c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

with the objective of ascertaining the safety and/or efficacy of those medicinal products (Article 2.2.1 of Regulation EU/2014/536).

‘Clinical trial’ means a clinical study which fulfils any of the following conditions:

(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

(c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.
‘Low-intervention clinical trial’ means a clinical trial which fulfils all of the following conditions:

(a) the investigational medicinal products, excluding placebos, are authorised;
(b) according to the protocol of the clinical trial,
   (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; 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;

‘Non-interventional study’ means a clinical study other than a clinical trial

‘Normal clinical practice’ means the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder

7.2 Sources of Risk to Patients

The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is particularly the case where the investigational medicinal product is covered by a marketing authorisation, that is the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure" or, if that product is not used in accordance with the terms of the marketing authorisation, that
use is evidence-based and supported by published scientific evidence on the safety and efficacy of that product, and the intervention poses only very limited additional risk to the subject compared to normal clinical practice (as per Recital 11 of Regulation EU/2014/536).

7.3 Risk Categories of Clinical Trials

The Recommendation of the Organisation for Economic Cooperation and Development (OECD) Council on the Governance of Clinical Trials of 10 December 2012 introduced different risk categories for clinical trials (Table 1). Those categories are compatible with the categories of clinical trials defined in this Regulation as the OECD Categories A and B(1) correspond to the definition of a low-intervention clinical trial (i.e., Pragmatic Clinical Trial) as set out in Regulation EU/2014/536, and the OECD Categories B(2) and C correspond to the definition of a clinical trial as set out in this Regulation (as per Recital 12 of Regulation EU/2014/536).

7.3.1 OECD Risk Categories

The three-category system proposed by the OECD, allows for good alignment of the requirements for international clinical trials (refer to Table 1 and Table 2): Category A roughly corresponds to the non-commercial (Non-IND, non-Chiken) trials outside of Europe, where no oversight by the regulatory authority is usually required. This will facilitate the independent assessment by academic institutions of medicinal products and treatment strategies, which is a critical activity for the optimization of healthcare and for cost containment. However, oversight by the regulatory authority is sometimes necessary for such post-marketing trials, in particular for clinical trials corresponding to post-marketing authorization commitments (part of the risk-management plan, post-authorisation safety or efficacy studies). This is made possible through the option of a notification to, or an approval by, the regulatory authority (as per the OECD Recommendation on the Governance of Clinical Trials, 2012).

Category A – Concerns clinical trials on authorised medicinal products (according to national or regional regulations) tested in accordance with their marketing authorisation (= Low Intervention Clinical Trial)

Category B – Concerns clinical trials on authorised medicinal products tested according to treatment regimens outside their marketing authorisation (in terms of population, condition, administration, or dosage):

1. Supported by published evidence or guidance or established medical practice (= Low Intervention Clinical Trial)
2. Not supported by published evidence or guidance or established medical practice (= Clinical Trial)
Category C – Concerns clinical trials on medicinal products without any marketing authorization (as per the OECD Recommendation on the Governance of Clinical Trials, 2012).

Table 1 – OECD Clinical Trial Risk Categories
(Source: OECD Recommendation on the Governance of Clinical Trials, 2012)

<table>
<thead>
<tr>
<th>Medicinal product</th>
<th>C – New product</th>
<th>B – Modified use</th>
<th>A – Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not authorised (according to national or regional regulation)</td>
<td>Authorised (according to national or regional regulation)</td>
<td>Authorised (according to national or regional regulation)</td>
</tr>
<tr>
<td>Based on Marketing Authorisation (MA) status, with modulating factors: (up/downgrade)</td>
<td>Tested according to treatment regimens outside the marketing authorisation (in terms of population, condition, administration, dosage)</td>
<td>(a) supported by or (b) not supported by published evidence and/or guidance and/or established medical practice</td>
<td>Tested in accordance with marketing authorisation</td>
</tr>
<tr>
<td>- Novelty (new chemical entity/class)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Innovative nature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MA in other countries</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2 – OECD Representation of International Clinical Trial Governance

(Source: [OECD Recommendation on the Governance of Clinical Trials, 2012](#))

<table>
<thead>
<tr>
<th>Marketing authorisation status of the medicinal products</th>
<th>Non-authorised medicine</th>
<th>Authorised medicine, treatment regimen outside marketing authorisation</th>
<th>Authorised medicine tested within marketing authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>IND trials Supervision by FDA Approval by IRB</td>
<td>Non-IND studies Approval by IRB</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Chiken trials Supervision by PMDA Approval by IRB</td>
<td>Non-chiken studies Approval by IRB</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>Exemption scheme Approval by RA (TGA) Approval by EC</td>
<td>Approval by RA Approval by EC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Notification scheme Approval by EC</td>
<td>Approval by RA (MHRA) (adaption of application dossier) Approval by EC</td>
<td></td>
</tr>
<tr>
<td>2001/20/EC Directive</td>
<td>Approval by RA Approval by EC</td>
<td>Approval by RA Approval by EC</td>
<td></td>
</tr>
<tr>
<td>UK adapted 2001/20/EC Directive</td>
<td>Approval by RA (MHRA) (adaption of application dossier) Approval by EC</td>
<td>Approval by RA (MHRA) (administration of application dossier) Approval by EC</td>
<td></td>
</tr>
<tr>
<td>Draft EU Regulation 2012</td>
<td>Co-ordinated approval by oversight bodies Low intervention trials Co-ordinated approval by oversight bodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OECD Recommendation</td>
<td>Approval by regulatory authority Approval by EC/IRB (adoption of application dossier) Approval by EC/IRB Approval by EC/IRB (Notification to or approval by RA as an option only)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Marketing authorisation**
- IND: Investigational new drug
- EC: Ethics committee
- IRB: Institutional review board
- RA: Regulatory authority
7.4 Low-Intervention Clinical Trials (Pragmatic Clinical Trials)

Low-intervention clinical trials (LICT) are often of crucial importance for assessing standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. Those clinical trials should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products. In order to ensure subject safety they should however be subject to the same application procedure as any other clinical trial. The published scientific evidence supporting the safety and efficacy of an investigational medicinal product not used in accordance with the terms of the marketing authorisation could include high quality data published in scientific journal articles, as well as national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence (as per Recital 11 of Regulation EU/2014/536).

Low-intervention clinical trials:

- Often of crucial importance for assessing standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health
- The investigational medicinal product is covered by a marketing authorisation i.e., the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure
- The intervention poses only very limited additional risk to the subject compared to normal clinical practice
- Should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products
- In order to ensure subject safety they should be subject to the same application procedure as any other clinical trial

Table 3 Illustrates where low-intervention clinical trials fit within the risk categorization implemented by Regulation EU/2014/536.
### Table 3 – Risk Categorization of ‘Low-Intervention Clinical Trials’

<table>
<thead>
<tr>
<th>C New Product</th>
<th>B Modified Use</th>
<th>A Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Authorised</td>
<td>(B2) Authorised</td>
<td>Authorised</td>
</tr>
<tr>
<td></td>
<td>Tested according to treatment regimens outside their marketing authorisation (in terms of population, condition, administration, or dosage)</td>
<td>Tested in accordance with marketing authorisation</td>
</tr>
<tr>
<td></td>
<td>Not supported by published evidence or guidance or established medical practice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supported by published evidence or guidance or established medical practice</td>
<td></td>
</tr>
<tr>
<td>Clinical Trial</td>
<td>Clinical Trial</td>
<td>Low-Intervention Clinical Trial</td>
</tr>
<tr>
<td></td>
<td>Low-Intervention Clinical Trial</td>
<td></td>
</tr>
</tbody>
</table>

### 7.5 Low-Intervention Trials will be Subject to Less Stringent Rules

Under [Regulation EU/2014/536](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32014R0536:EN:HTML), low-intervention clinical trials will be subject to less stringent rules (relative to higher risk clinical trials), such that:

- **IB/SmPC** - If the investigational medicinal product is authorised, and is used in accordance with the terms of the marketing authorisation, the approved summary of product characteristics (SmPC) shall be the IB (as per Annex I.E.28 of [Regulation EU/2014/536](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32014R0536:EN:HTML))

- **IMPD** - The applicant may submit the version of the SmPC valid at the time of application, as the IMPD if the investigational medicinal product is authorized (as per Annex I.G.52 of [Regulation EU/2014/536](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32014R0536:EN:HTML))

- **Damage Compensation** - Member States shall not require any additional systems for compensation from the sponsor of low-intervention clinical trials (as per Article 76.3 of [Regulation EU/2014/536](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32014R0536:EN:HTML))

- **TMF** - The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the
quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial (as per Article 57 of Regulation EU/2014/536)

- **IMP** - Investigational medicinal products shall be traceable. They shall be stored, returned and/or destroyed as appropriate and proportionate to ensure the safety of the subject and the reliability and robustness of the data generated in the clinical trial, in particular, taking into account whether the investigational medicinal product is an authorised investigational medicinal product, and whether the clinical trial is a low-intervention clinical trial (as per Article 51 of Regulation EU/2014/536).

- **IMP Labelling** - The following should appear on the immediate and the outer packaging of authorized investigational medicinal products:
  - Name of the main contact;
  - Clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject;
  - 'For clinical trial use only' or similar wording (as per Annex VI, paragraph 7 of Regulation EU/536/2014).

- **Monitoring** - The extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment that takes into consideration all characteristics of the clinical trial, including the following characteristics:
  - whether the clinical trial is a low-intervention clinical trial;
  - the objective and methodology of the clinical trial; and
  - the degree of deviation of the intervention from normal clinical practice (as per Article 48 of Regulation EU/2014/536).

- **Simplified Consent (Single-Country Low-Intervention Cluster Trials)** - It is appropriate to allow that informed consent be obtained by simplified means for certain clinical trials where the methodology of the trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products (as per Article 30, Recital 33 and Annex I.L.62 of Regulation EU/2014/536).

### 7.6 Risk-Based Consent?

#### 7.6.1 Simplified Consent for Single-Country Cluster Trials

According to Regulation EU/2014/536, it is appropriate to allow that informed consent be obtained by simplified means for certain clinical trials where the methodology of the trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products (Figure 3). In those clinical trials the
investigational medicinal products are used in accordance with the marketing authorisations, and the individual subject receives a standard treatment regardless of whether he or she accepts or refuses to participate in the clinical trial, or withdraws from it, so that the only consequence of non-participation is that data relating to him or her are not used for the clinical trial. Such clinical trials, which serve to compare established treatments, should always be conducted within a single Member State (Recital 33 of Regulation EU/2014/536).

**Definition: Cluster Trial**

A form of randomised controlled trial in which entire groups of participants (i.e., clusters), instead of individual participants are randomised. It is used to reduce the risk of contamination between participants receiving the experimental and control intervention.


**Definition: Cluster Sampling**

A sampling method in which each unit selected in a group of persons (all persons in a city block, a family etc) rather than an individual.

7.7 Considerations when Implementing Simplified Consent – UK Position

In November 2014, the UK’s Health Research Authority (HRA) released a consultation document to seek comments on proposed HRA guidance on simpler procedures for seeking consent from patients to take part in large-scale simple and efficient research trials within the NHS. The response to the consultation was published in July 2015:


7.7.1 Why is it Important to Conduct Such Trials?


In many cases we don't always know (due to a lack of evidence) which of the large number of treatments routinely used in the NHS is best for an individual patient, or
group of patients. It’s important, therefore, to compare the medicines and other treatments used in order to better inform evidence-based treatment.

The best way to get the evidence is to carry out large scale research with the help of patients who are willing to agree to take part so that we can reliably compare the different treatments available. This can be costly and time-consuming.

However, such trials could be carried out more simply and efficiently by recruiting patients into the research at the time they are prescribed their medicine or treatment at the GP Surgery or hospital.

These trials often referred to as “pragmatic trials”, are cheaper to run than large-scale drug trials and present little or no risk to the participant as they would receive a standard treatment routinely prescribed within the NHS for their condition. In many cases this will be exactly the same treatment they would receive if they declined to take part in the research. The patients recruited to these trials can be followed up through their electronic health records held by their GP or, where applicable, their hospital medical records. For the vast majority of these types of trials the patient would not be asked to do anything other than agree to be randomised (rather like tossing a coin or rolling a die) to a standard treatment and to the use of their data for purposes of the research. For some trials it might also be necessary to ask them to agree to some additional research procedures such as extra blood tests or answering a simple questionnaire.

These 'simple and efficient trials' can be randomised in two ways:

- Individual randomisation where each patient who is suitable to join the trial will be individually allocated to an intervention, or
- Cluster randomisation where separate GP practices, wards, or hospitals are randomised to provide different interventions.

This latter type of trial is called a cluster randomised trial or 'cluster trial’ for short.

A forthcoming piece of European legislation (the ‘Clinical Trials Regulation’ likely to come into force in 2016/2017) will allow informed consent to be obtained in cluster trials involving drugs by what it refers to as 'simplified means'. Whilst this EU Regulation is not yet applicable to drug trials we need to consider what the practical and ethical implications of this important provision are now so that that we are able to provide appropriate guidance regarding the seeking of consent by simplified means once this Regulation is in force.

### 7.7.2 Why do we Need Guidance on Seeking Consent for Such Trials?


'Simple and efficient’ trials could involve routine interventions ranging from testing hospital mattresses to comparing licensed medicines. Whilst trials involving mattresses or other non-drug interventions only need to comply with what is known as the
“common law”, research involving medicines also needs to comply with complex legal regulations (known as The Clinical Trials Regulations) setting out in detail how patients should be recruited to such trials in the U.K. In order to comply with these regulations patients recruited to them must have had the nature, significance, implications and risks of the trial explained to them in a ‘prior interview’ with a member of the investigating team. These Regulations apply to all drug trials, where the drug the patient receives is decided by the research protocol rather than their doctor, regardless of whether they are looking at a completely new experimental medicine or comparing medicines that have been shown to be safe and are already in routine use.

We believe guidance is needed in order to facilitate simple and efficient trials looking at the effectiveness of routinely used standard treatments so that patients can be recruited in a way that complies with the law but does not overly burden either the patient or the health care professional seeking consent. Central to this more proportionate approach is the use of a suggested short information sheet template.

7.7.3 Suggested Specific Principles Regarding Seeking Consent in Simple and Efficient Trials


The HRA suggest that simplified consent procedures may be used in line with the following principles:

- Following the normal consent process would place a disproportionate burden in terms of time and resources in relation to the perceived risk
- The study addresses a clinical question where there is uncertainty regarding the relative merits of relevant interventions
- All medicines used in the trial are in routine use and within the terms of their licence
- The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research-specific laboratory tests, study visits, questionnaires etc.)
- All interventions/diagnostic tests are in routine use within the NHS and will be undertaken by those qualified to do so
- Research risks are no greater than those involved in standard care/not greater than minimal (e.g. extra blood tests/tissue samples taken during a ‘clinically directed’ procedure)
- The use of simplified means to obtain consent does not adversely affect the rights or welfare of study participants
• Healthcare Professionals (HCPs) have the option of using an intervention other than the one assigned if they believe doing so is important for a particular patient
• Patient has not expressed a strong preference for any particular treatment

7.7.4 Simplified Consent Scenarios


**SCENARIO 1 - EXPLICIT CONSENT (SHORT INFORMATION SHEET)**

**Clinical trial of Statins (GP Surgery)**

**Scenario:** Comparison of licenced statins to reduce low-density lipoprotein (LDL) cholesterol - Individual Patient Randomisation

**NHS context:** Primary Care (General Practice)

**Key factors:**

• The drug that the patient would receive is decided by the research protocol (randomised) and not the GP
• This is a Clinical Trial of Investigational Medicinal Products (CTIMP)
• All trial drugs are licenced and in routine use in the NHS
• There is insufficient evidence regarding comparative effectiveness
• Systematic reviews have been conducted and genuine uncertainty exists regarding which medicine is best
• Participants will know what drug they have been given – Relevant medicine ‘patient information leaflets’ (PIL) are available and provided to patients with their medicine as normal.
• Only routine clinical data will be collected
• Patients are not subjected to any risk greater than those related to standard care
• The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research-specific laboratory tests, study visits, questionnaires etc.)

**Possible consent option: Explicit consent sought by GP/ Other Health Care Professional (HCP)**

HCP verbally explains to patient that:
• We have agreed that you would benefit from a treatment with a statin. However, there is uncertainty amongst doctors regarding which licensed statin is best.
• We wish to find out which one works best by asking you to take part in a research trial.
• HCP gives patient short Participant Information Sheet including link to further online information.
• HCP asks the patient if they have any questions.
• If patient agrees, on basis of verbal explanation/PIS, their consent documented in patient electronic records by HCP (GP/Practice Nurse/Pharmacist)
• Patient signs paper consent document

HRA Response to Consultation Feedback
There is cautious but encouraging support for the use of a ‘short information sheet’ for simple and efficient trials, in conjunction with asking if potential participants have any questions, before explicitly confirming consent to take part in a simple trial. However, many respondents raised practical issues around the time that could be set aside for the “interview” and the need not to place undue pressure on patients to take part in research. The final guidance will incorporate a short information sheet template for use in simple and efficient trials and will highlight potential pressures to take part and practical methods for dealing with these.

SCENARIO 2 - ‘DEEMED’ CONSENT (OPT-OUT) - PATIENT ASKED TO CONFIRM CONSENT
Randomised Cluster Trial (GP Surgery)
Scenario: Comparison of licenced statins to reduce low-density lipoprotein (LDL) cholesterol - Cluster trial – Randomisation at GP Clinic level
NHS context: Primary Care (General Practice)
Key factors:
• The GP practice is the unit of randomisation i.e. whilst different GP surgeries will prescribe different drugs in the trial all eligible patients within a single GP surgery will be given the same drug
• This is a Clinical Trial of Investigational Medicinal Products (CTIMP)
• All trial drugs are licenced and in routine use in the NHS
• There is insufficient evidence regarding comparative effectiveness
• Systematic reviews have been conducted and genuine uncertainty exists regarding which medicine is best
• Participants will know what drug they have been given – Relevant medicine ‘patient information leaflets’ (PIL) are available and provided to patients with their medicine as normal.
• Only routine clinical data will be collected
• Patients are not subjected to any risk greater than those related to standard care
• The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research- specific laboratory tests, study visits, questionnaires etc.)

**Possible consent option: Implicit/Deemed consent (opt-out) - Confirmed**

- Poster on prominent display in GP surgery waiting room explaining that a trial of statins is taking place. The poster contains information equivalent to the information provided in the example short Participant Information Sheet (see para 2.7). This includes a web address for further online information. Translated versions of the poster used as necessary.
- Paper copies of the information sheet are available on request.
- Poster includes explanation that all patients will be included in the trial if they need to be prescribed a statin and meet the inclusion criteria UNLESS they explicitly inform the GP or other surgery staff that they do not wish to take part (i.e. Opt-Out).
- During consultation with patient HCP reiterates that unless the patient disagrees (opts-out) they will be included in a clinical trial and their treatment determined at random between existing routine treatments. HCP explains where further information can be obtained (e.g. short information sheet/website).

**HRA Response to Consultation Feedback**

There is very little support amongst respondents for the use of posters as the only method used to inform potential participants. The use of posters on their own will not be endorsed in the final guidance for use in clinical trials (drug trials).

**SCENARIO 3 - ‘DEEMED’ CONSENT (OPT-OUT) – PATIENT NOT ASKED TO CONFIRM CONSENT**

**Randomised Cluster Trial (GP Surgery)**

**Scenario:** Comparison of licenced statins to reduce low-density lipoprotein (LDL) cholesterol - Cluster trial – Randomisation at GP Clinic level

**NHS context:** Primary Care (General Practice)

**Key factors:**
• The GP practice is the unit of randomisation i.e. whilst different GP surgeries will prescribe different drugs in the trial all eligible patients within a single GP surgery will be given the same drug
• This is a Clinical Trial of Investigational Medicinal Products (CTIMP)
• All trial drugs are licenced and in routine use in the NHS
• There is insufficient evidence regarding comparative effectiveness
• Systematic reviews have been conducted and genuine uncertainty exists regarding which medicine is best
• Participants will know what drug they have been given – Relevant medicine ‘patient information leaflets’ (PIL) are available and provided to patients with their medicine as normal.
• Only routine clinical data will be collected
• Patients are not subjected to any risk greater than those related to standard care
• The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research-specific laboratory tests, study visits, questionnaires etc.)

Possible consent option: ‘Deemed’ consent (opt-out) – Patient not asked to confirm consent
• Poster on prominent display in GP surgery waiting room explaining that a trial of statins is taking place. The poster contains information equivalent to the information provided in the example short Participant Information Sheet (see para 2.7). This includes a web address for further online information. Translated versions of the poster used as necessary.
• Paper copies of the information sheet are available on request.
• Poster includes explanation that all patients will be included in the trial if they need to be prescribed a statin and meet the inclusion criteria UNLESS they explicitly inform the GP or other surgery staff that they do not wish to take part (i.e. Opt-Out).
• HCP enrols patient if they meet the inclusion criteria but DOES NOT provide any further information (either written or verbal) regarding research component nor seek explicit consent from the patient.
• HCP documents patient enrolment into trial along with all refusals and withdrawals. (NB this option would not be legal under the current Clinical Trials Regulations but might be permitted by the forthcoming EU Clinical Trial Regulation – see para 3.6)
The majority of respondents rejected the suggestion that the use of a poster alone could constitute information being “given” to a potential research participant in the context of a cluster randomised drug trial. In doing so, a large number cited that it was unlikely that patients would notice or read any such poster. Some suggested any use of posters would always need to be backed up by other direct methods of information provision.

The revised guidance will not endorse the use of posters without additional direct methods of ensuring that information is provided to potential participants.

The concept of ‘deemed consent’ received little support in the context of randomised cluster trials, however when combined with asking the patient whether they would wish to decline taking part a majority felt that this would be acceptable. It is arguable if such an approach is truly an ‘opt-out’ model and might be better understood as support for ‘opt-in’ procedures involving explicit consent, particularly given the majority rejection of posters alone as a method of information provision.

Deemed consent, where patients are not asked whether they would prefer to withdraw from the trial, will not be endorsed in final guidance in circumstances where it is possible and practical to seek explicit consent.

As ‘deemed’ consent in the context of randomised cluster trials involving medicines will only be legally acceptable once the EU Clinical Trials Regulation comes into force the HRA will not publish guidance regarding its use until that time.
8 About the Author

Stuart McCully is the owner and founder of CHCUK Ltd, which he created in 2009 to help companies and organisations understand the regulatory requirements for non-interventional and real world studies, a gap/need he saw in the market at the time.

Stuart has a BSc and PhD in Pharmacology and has worked in regulatory compliance roles since 2000 in the Pharmaceutical and CRO industries.

Stuart also currently leads the NIS Regulatory Intelligence team at inVentiv Health Clinical…a man of many hats!

Contact: stuart.mccully@chcuk.co.uk
9 Useful Links

9.1 Regulatory Bodies

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<td>Health Research Authority (HRA)</td>
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<td>Organisation for Economic Cooperation and Development (OECD)</td>
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9.2 Literature References

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<td>Anderson et al., 2015 - The Food and Drug Administration and pragmatic clinical trials of marketed medical products. Clin Trials October 2015 vol. 12 no. 5 511-519</td>
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<td>Loudon et al., 2015 - Loudon Kirsty, Treweek Shaun, Sullivan Frank, Donnan Peter, Thorpe Kevin E, Zwarenstein Merrick et al. The PRECIS-2 tool: designing trials that are fit for purpose BMJ 2015;350:h2147</td>
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<td>McGraw et al., 2015 - Privacy and confidentiality in pragmatic clinical trials. Clin Trials October 2015 vol. 12 no. 5 520-529</td>
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<td>O’Rourke et al., 2015 - Harmonization and streamlining of research oversight for pragmatic clinical trials. Clin Trials October 2015 vol. 12 no. 5 449-456</td>
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<td>Smalley et al., 2015 - Ethical responsibilities toward indirect and collateral participants in pragmatic clinical trials. Clin Trials October 2015 vol. 12 no. 5 476-484</td>
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<td>Welch et al., 2015 - The ethics and regulatory landscape of including vulnerable populations in pragmatic clinical trials. Clin Trials October 2015 vol. 12 no. 5 503-510</td>
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### 9.3 Consultation Documents

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### 9.4 Legislation

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### 9.5 Guidelines and Recommendations

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### 10 Glossary

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<td>Authorised Investigational Medicinal Product</td>
<td>‘Authorised investigational medicinal product’ means a medicinal product authorised in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product. (Article 2.2.9 of Regulation EU/2014/536)</td>
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| Clinical Study                            | ‘Clinical study’ means any investigation in relation to humans intended:  
  a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;  
  b) to identify any adverse reactions to one or more medicinal products; or  
  c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;  
  with the objective of ascertaining the safety and/or efficacy of those medicinal products. (Article 2.2.1 of Regulation EU/2014/536) |
| Clinical Trial                            | ‘Clinical trial’ means a clinical study which fulfils any of the following conditions:  
  (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;  
  (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or  
  (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects. (Article 2.2.2 of Regulation EU/2014/536) |
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<tr>
<td>administrative provisions of the Member States relating to the</td>
<td>implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use</td>
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<td>Cluster Trial/ Cluster Randomised Controlled Trial</td>
<td>A form of randomised controlled trial in which entire groups of participants (i.e., clusters), instead of individual participants are randomised. It is used to reduce the risk of contamination between participants receiving the experimental and control intervention. (A Dictionary of Epidemiology, Sixth Edition, 2014. Ed. Miquel Porta. Oxford University Press)</td>
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<td>Explanatory Trial/ Study</td>
<td>A study whose main objective is to ascertain some preliminary facts or to familiarize researchers with a problem or technology, often without a clear or precise hypothesis; or, sometimes, to screen several hypotheses at once in a preliminary fashion. (A Dictionary of Epidemiology, Sixth Edition, 2014. Ed. Miquel Porta. Oxford University Press)</td>
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<td>Investigational Medicinal Product (IMP)</td>
<td>‘Investigational medicinal product’ means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial. (Article 2.2.5 of Regulation EU/2014/536)</td>
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| Low-Intervention Clinical Trial (LICT)                              | ‘Low-intervention clinical trial’ means a clinical trial which fulfils all of the following conditions: (d) the investigational medicinal products,
### Term

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<td>excluding placebos, are authorised;</td>
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<td>(e) according to the protocol of the clinical trial,</td>
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<td>(iii) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or</td>
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<td>(iv) 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</td>
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<td>(f) 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;</td>
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<th>Non-Interventional Study (NIS)</th>
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<td>‘Non-interventional study’ means a clinical study other than a clinical trial.</td>
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<td>Non-Interventional Study or Non-Interventional Trial: a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.</td>
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<td>(Article 2(c) of 2001/20/EC – The EU Clinical Trials Directive)</td>
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<td>‘Normal clinical practice’ means the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder.</td>
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**Term** | **Definition**
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Observational Study | Refer to ‘Non-Interventional Study (NIS)’
Organisation for Economic Cooperation and Development (OECD) | The OECD provides a forum in which governments can work together to share experiences and seek solutions to common problems. We work with governments to understand what drives economic, social and environmental change. We measure productivity and global flows of trade and investment. We analyse and compare data to predict future trends. We set international standards on a wide range of things, from agriculture and tax to the safety of chemicals.
http://www.oecd.org/
Pragmatic Clinical Trial (PCT) | A study (including randomized clinical trials) whose aim is to determine the effects of an intervention under the usual conditions in which it will be applied. By contrast with an EXPLANATORY STUDY, the focus is on guiding decision e.g., about healthcare.
Pragmatic Clinical Trial – New Definition? | Califf *et al.*, (2015) propose three key attributes of PCTs:
1) An intent to inform decision-makers (patients, clinicians, administrators, and policy-makers), as opposed to elucidating a biological or social mechanism;
2) An intent to enroll a population relevant to the decision in practice and representative of the patients or populations and clinical settings for whom the decision is relevant; and
3) Either an intent to:
   a. streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial, or
   b. measure a broad range of outcomes
Given these attributes, a common-sense definition for a PCT would thus be as follows:
"Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or
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<td>‘behavioral health intervention at the individual or population level’</td>
<td>(Califf et al., 2015)</td>
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