



2026 KCE Trials calls: information session

Pragmatic Trials

PRAGMATIC TRIALS

Many questions in healthcare are currently not sufficiently studied in clinical trials, despite their high societal importance (e.g. comparison between medication and surgery, between different surgical techniques, between lifestyle changes and a medical intervention, or questions addressing the needs of older people). **'Comparative effectiveness' studies compare two treatment options (with 'no treatment' being one of the possible treatment options) that are already in use in clinical practice in a given indication, but are not yet sufficiently directly compared (i.e. which of the two treatment options works best in daily practice and is the most cost-effective).** Since 2015, KCE is managing a national funding programme of such pragmatic practice-oriented clinical trials, the KCE Trials Programme. The annual budget is 9.5 € Million.

Design

- The study design would answer the research question proposed.
- A **pragmatic** design is to be selected if this would be most informative.
- Trial design should allow for sufficiently long follow-up.
- A randomised, multicentre design is mandatory.
- Sample size should be correct and well justified.



PRAGMATIC TRIALS

Studies comparing two treatment options that are already in use in clinical practice

All types of interventions (“strategy”)

Which of the two treatment options work best in daily practice?



Definitions

- Schwartz and Lellouch (J. Chron. Dis.1967;20:637-48)
([republished 2009](#))
 - Explanatory trials = to test causal research hypotheses (“Can it work?”)
 - Pragmatic trials = to help choose between care options (“Does it work?”)
- Roland M ([BMJ 1998;316:285](#))
 - Pragmatic trials measure **effectiveness**—the benefit the treatment produces in routine clinical practice
 - Explanatory trials generally measure **efficacy**—the benefit a treatment produces under ideal conditions

© Prof. Sandra Eldridge



EXPLANATORY

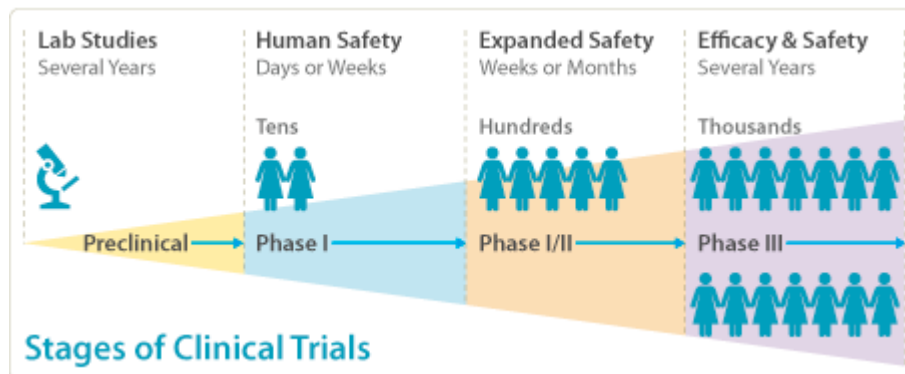
In this multicenter, double-blind, parallel-group, phase 3 trial, we randomly assigned participants with relapsing or refractory eosinophilic granulomatosis with polyangiitis who had received treatment for at least 4 weeks and were taking a stable prednisolone or prednisone dose to receive 300 mg of mepolizumab or placebo,

Leukemia. 2017 Jun 13. doi: 10.1038/leu.2017.186. [Epub ahead of print]

A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia.

Santini V^{1,2}, Allione B^{2,3}, Zini G^{2,4}, Gioia D², Lunghi M^{2,5}, Poloni A^{2,6}, Cilloni D^{2,7}, Sanna A^{2,8}, Masiera E², Ceccarelli M^{2,9}, Abdel-Wahab O^{2,10}, Terenzi A^{2,11}, Angelucci E^{2,12}, Finelli C^{2,13}, Onida F^{2,14}, Pelizzari AM^{2,15}, Ferrero D^{2,16}, Saglio G^{2,17}, Figueroa M¹⁸, Levis A².

Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial.



We conducted three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in adults with ulcerative colitis. In the OCTAVE Induction 1 and 2 trials, 598 and 541 patients, respectively, who had moderately to severely active ulcerative colitis despite previous conventional therapy or therapy with a tumor necrosis factor antagonist were randomly assigned to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8



Pragmatic

[Lancet](#). 2016 May 21;387(10033):2117-24. doi: 10.1016/S0140-6736(16)00548-1. Epub 2016 Mar 2.

Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial.

[van Vliet EO](#)¹, [Nijman TA](#)¹, [Schuit E](#)², [Heida KY](#)¹, [Opmeer BC](#)³, [Kok M](#)⁴, [Gyselaers W](#)⁵, [Porath MM](#)⁶, [Woiski M](#)⁷, [Bax CJ](#)⁸, [Bloemenkamp KW](#)⁹, [Scheepers HC](#)¹⁰, [Jacquemyn Y](#)¹¹, [van Beek E](#)¹², [Duvekot JJ](#)¹³, [Franssen MT](#)¹⁴, [Papatsonis DN](#)¹⁵, [Kok JH](#)¹⁶, [van der Post JA](#)⁴, [Franx A](#)¹, [Mol BW](#)¹⁷, [Oudijk MA](#)¹⁸.

[Chiropr Man Therap](#). 2017 Apr 28;25:12. doi: 10.1186/s12998-017-0141-3. eCollection 2017.

Manual therapy compared with physical therapy in patients with non-specific neck pain: a randomized controlled trial.

[Groeneweg R](#)^{1,2,3}, [van Assen L](#)¹, [Kropman H](#)³, [Leopold H](#)³, [Mulder J](#)¹, [Smits-Engelsman BCM](#)⁴, [Ostelo RWJG](#)^{2,5}, [Oostendorp RAB](#)^{1,6}, [van Tulder MW](#)².

 **Author information**

[Health Technol Assess](#). 2017 Apr;21(20):1-278. doi: 10.3310/hta21200.

A cluster randomised trial, cost-effectiveness analysis and psychosocial evaluation of insulin pump therapy compared with multiple injections during flexible intensive insulin therapy for type 1 diabetes: the REPOSE Trial.

[Heller S](#)¹, [White D](#)², [Lee E](#)², [Lawton J](#)³, [Pollard D](#)⁴, [Waugh N](#)⁵, [Amiel S](#)⁶, [Barnard K](#)⁷, [Beckwith A](#)⁸, [Brennan A](#)⁴, [Campbell M](#)⁴, [Cooper C](#)², [Dimairo M](#)², [Dixon S](#)⁴, [Elliott J](#)¹, [Evans M](#)^{9,10}, [Green F](#)¹¹, [Hackney G](#)², [Hammond P](#)¹², [Hallowell N](#)³, [Jaap A](#)¹³, [Kennon B](#)¹⁴, [Kirkham J](#)³, [Lindsay R](#)¹⁵, [Mansell P](#)¹⁶, [Papaioannou D](#)², [Rankin D](#)³, [Royle P](#)⁵, [Smithson WH](#)¹⁷, [Taylor C](#)¹⁸.

[Trials](#). 2011 Jan 27;12:24. doi: 10.1186/1745-6215-12-24.

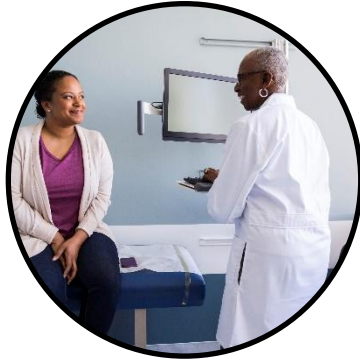
Comparing the effect of hydroxyethyl starch 130/0.4 with balanced crystalloid solution on mortality and kidney failure in patients with severe sepsis (6S--Scandinavian Starch for Severe Sepsis/Septic Shock trial): study protocol, design and rationale for a double-blinded, randomised clinical trial.



	Explanatory	Pragmatic
Patients	Highly selected participants	Representative participants
Interventions	Intervention requires additional resources	Interventions slotted into usual care
Delivery	Very standardised delivery, highly controlled adherence	Flexibility in delivery and adherence
Follow-up	More extensive follow-up	Follow-up = usual care
Outcomes	Surrogate outcomes	Patient centred outcomes



ELIGIBILITY CRITERIA



**Patients in trial
should be
representative for
target group of
intervention**



**Broad eligibility
criteria e.g. no
exclusion based on
co-morbidity,
age,...**



Do not copy-paste!



- Pragmatic STAR*D trial: only 22% eligible for phase III explanatory trials

Results | Between January 2013 and September 2014, 28 454 PINNACLE patients with ACS at 182 practices were identified. Of these, 10 228 (35.9%) met IMPROVE-IT criteria (**Figure**), with modest variation between practices (median 34.5%; IQR, 25.6-42.9). Compared with IMPROVE-IT patients, PINNACLE patients were significantly older, more likely female, had mark-

Results: Among 319 ongoing RCTs, despite the high prevalence of the concomitant chronic conditions, patients with these conditions were excluded in 251 trials (79%). For example, although 91% of patients with CHD had a concomitant chronic condition, 69% of trials targeting such patients excluded patients with concomitant chronic condition(s). When considering

RESULTS: Overall, patients included in the LPCS were younger (mean difference (MD)-2.4; p=0.03), predominantly male (MD 12.4; p=0.1) with worse lung function (FEV1% MD -16.4; p<0.01) and worse quality of life scores (SGRQ MD 15.8; p=0.01). There were large differences in GOLD stage distribution compared to primary care patients. Mean exacerbation rates were higher in LPCS, with an overrepresentation of patients with ≥ 1 and ≥ 2 exacerbations, although results were not statistically significant. Our findings add to the literature, as we revealed hitherto unknown GOLD I exacerbation characteristics, showing 34% of mild patients had ≥ 1 exacerbations per year and 12% had ≥ 2 exacerbations per year. The proportion of primary care patients eligible for inclusion in LPCS ranged from 17% (TRISTAN) to 42% (ECLIPSE, UPLIFT).



Eligibility

Try to include all eligible patients

- **Limit additional work, e.g. electronic data collection with limited number of variables PROMs, research nurses, local FU**
- **Informed consent and modes of communication**
- **Reimbursement of costs for patients, e.g. transport**
- **Involve patient representatives!**



Site selection



Setting e.g. first line vs second line

Site selection: mixture, 'typical' sites e.g. not only high-volume sites



Smaller sites often lack infrastructure and experience but can be more representative

Feasibility of the protocol



Site initiation and (financial) support



OUTCOMES

- Ideal outcome: full impact of a treatment on patients' health: Benefits and harms
- Outcomes important for patients, health care professionals and policy makers, payers
- Typical outcomes include mortality, morbidity, functional status, QoL, resource use



- **Primary outcome:** the outcome that will make you use/implement/reimburse the intervention (or not).
“Outcome most influential for the clinical decision”
- Patient reported outcomes (PROs):
no interpretation by others needed
- Use validated instruments
- Involve patients in your trial design!



CONSIDERATIONS

- Feasibility, measurability
- Interference with usual practice
- Cave surrogate outcomes (do not copy-paste!): “accepted by FDA” versus “important for patients”



- Timepoint clearly defined
- Consider long-term follow-up
- Consider routinely collected data, electronic health records
- Interpretation should be easy and clinically relevant



Jeremy Grimshaw @GrimshawJeremy · 3m

2. 2015 Cochrane review tinyurl.com/ydf6z7r9 showed very weak evidence that ketamine might have benefit at 1 wk but unclear at 2 wks.

Theresa Boyle @theresaboyle

There's More Proof That #Ketamine Works for #Depression ti.me/2t0T3Wo



CORE OUTCOME SETS

- **Developed together with different stakeholders**
- **Consistent measurement of relevant outcomes in clinical trials**
- **Enables comparison of study results**



COMET

- The Core Outcome Measures in Effectiveness Trials
- www.comet-initiative.org

 **Search COMET database**

The COMET database currently contains **891** references of planned, ongoing and completed work.

Search

The keyword used for the search will be compared with study title, abstract and author's surname.

[View full search options](#)

To view a demonstration of how to search the COMET database click [here](#)

 **Core resource pack**

Useful references for core outcome set developers.

This includes an overview of the problems with outcomes in trials, key issues to consider in the development of a core outcome set, examples of core outcome set development, and things to think about once a COS is agreed. To read more, click [here](#).



Search results

Found 1 matching study

 [Submit search results enquiry](#)

	Study Title	Year	Disease Category	Disease Name	Study Type	View
☒	Report from the multinational irritable bowel syndrome initiative 2012 <i>Pimentel, M. Talley, N. J. Quigley, E. M...</i>	2013	Gastroenterology	Irritable bowel syndrome (IBS)	COS for clinical trials or clinical research	

Abstract:

In 2012, a group of 29 internationally recognized experts in the pathophysiology, diagnosis, and treatment of irritable bowel syndrome (IBS) convened to audit the current state of IBS research. The meeting was preceded by a comprehensive online survey that focused on research needs for IBS diagnosis (particularly the strengths and shortcomings of current criteria), definitions used in clinical trials for IBS patients and "healthy controls," potential biomarkers for IBS, and outcome measures in drug trials. While the purpose of the meeting was not to make binding recommendations, participants developed a framework for future questions and research needs in IBS. First, participants indicated the need for revised criteria for the diagnosis of IBS; in particular, inclusion of bloating and de-emphasis of pain as criteria were considered critical needs. Second, participants noted that definitions of normal, healthy controls varied widely among clinical trials; these definitions need to be standardized not only to improve the reliability of results, but also to better facilitate inter-trial comparisons and data synthesis. Third, participants highlighted the need for accurate biomarkers of disease. Fourth and finally, participants noted that further defining outcome measures, so that they are functionally relevant and reflect normalization of bowel function, is a critical need. Together, the discussions held at this workshop form a framework to address future research in IBS.



ICHOM

- International Consortium for Health Outcomes Measurement (ICHOM)
- www.ichom.org

OUR STANDARD SETS

By 2017, we aim to have published Standard Sets covering more than 50 percent of the global disease burden.

COMPLETED CONDITIONS

All 21	Cardiovascular 3	Congenital anomalies 2	Digestive 1	Malignant neoplasms 5	Maternal and neonatal 1	Mental and behavioral disorders 1
Musculoskeletal 2	Neurological 2	Primary/preventative care 1	Sense organ 2	Urogenital 1		



Pregnancy and Childbirth
Maternal and neonatal



Inflammatory Bowel Disease
Digestive



Overactive Bladder
Urogenital



Colorectal Cancer
Malignant Neoplasms



HEART FAILURE

The ICHOM Standard Set for Heart failure is the result of hard work by a group of leading physicians, measurement experts and patients. It is our recommendation of the outcomes that matter most to persons with Heart failure. We urge all providers around the world to start measuring these outcomes to better understand how to improve the lives of their patients.

- 1 Includes dyspnoea, fatigue and tiredness, disturbed sleep, and peripheral oedema.
- 2 Includes health-related quality of life, maximum physical exertion.
- 3 Includes depression and anxiety, confidence and self-esteem.
- 4 Includes admissions, appointments.



REFERENCE GUIDE

A complete overview of the ICHOM Standard Set, including definitions for each measure and selected PROM instruments, time points for collection, and associated risk factors is available here:



Version 1.0.4: May 2nd, 2017



PRAGMATIC TRIALS

- Pragmatic is not synonym to “easy to conduct” or “sloppy” !!!!
 - Data quality
 - Consent
 - Regulatory
 - Safety
 - Timelines
 - No substandard care



CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

Kenneth F Schulz,¹ Douglas G Altman,² David Moher,³ for the CONSORT Group

CONSORT 2010

The CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline is intended to improve the reporting of parallel-group randomized controlled trial (RCT), enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results. This can only be achieved through complete adherence and transparency by authors.

Improving the reporting of pragmatic trials: an extension of the CONSORT statement

Merrick Zwarenstein,¹²³ Shaun Treweek,⁴⁵ Joel J Gagnier⁵⁶ Douglas G Altman,⁷ Sean Tunis,⁸⁹¹⁰ Brian Haynes,¹¹ Andrew D Oxman,⁵ David Moher,¹²¹³ for the CONSORT and Pragmatic Trials in Healthcare (Practihc) groups

Pragmatic trials are designed to inform decisions about practice, but poor reporting can reduce their usefulness. The **CONSORT and Practihc groups** describe modifications to the CONSORT guidelines to help readers assess the applicability of the results

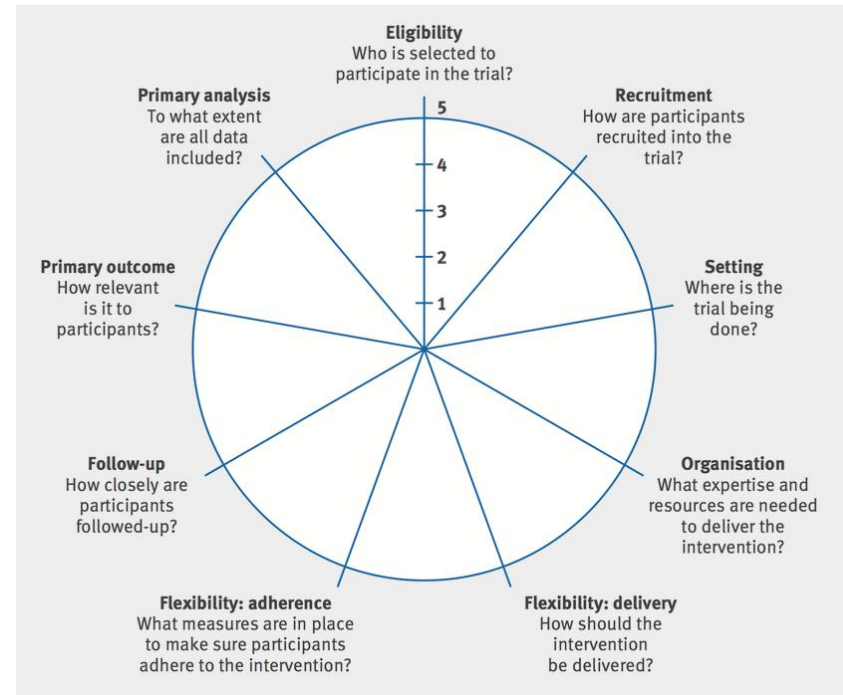


Section	Item	Standard CONSORT description	Extension for pragmatic trials
Title and abstract	1	How participants were allocated to interventions (eg, “random allocation,” “randomised,” or “randomly assigned”)	
Introduction			
Background	2	Scientific background and explanation of rationale	Describe the health or health service problem that the intervention is intended to address and other interventions that may commonly be aimed at this problem
Methods			
Participants	3	Eligibility criteria for participants; settings and locations where the data were collected	Eligibility criteria should be explicitly framed to show the degree to which they include typical participants and/or, where applicable, typical providers (eg, nurses), institutions (eg, hospitals), communities (or localities eg, towns) and settings of care (eg, different healthcare financing systems)
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	Describe extra resources added to (or resources removed from) usual settings in order to implement intervention. Indicate if efforts were made to standardise the intervention or if the intervention and its delivery were allowed to vary between participants, practitioners, or study sites Describe the comparator in similar detail to the intervention
Objectives	5	Specific objectives and hypotheses	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors)	Explain why the chosen outcomes and, when relevant, the length of follow-up are considered important to those who will use the results of the trial
Sample size	7	How sample size was determined; explanation of any interim analyses and stopping rules when applicable	If calculated using the smallest difference considered important by the target decision maker audience (the minimally important difference) then report where this difference was obtained
Blinding (masking)	11	Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment	If blinding was not done, or was not possible, explain why
Statistical methods	12	Statistical methods used to compare groups for primary outcomes; methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended)—specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome; describe deviations from planned study protocol, together with reasons	The number of participants or units approached to take part in the trial, the number which were eligible, and reasons for non-participation should be reported



PRECIS-2

Designing clinical trials is challenging. PRECIS – PRagmatic Explanatory Continuum Indicator Summary – is a clever acronym for a tool to help trialists designing clinical trials consider where they would like their trial to be on the pragmatic/explanatory continuum.



TAKE HOME MESSAGES

- ◆ **Pragmatic trial: benefit/harm in routine clinical practice**
- ◆ **Approach to trial design: eligibility, recruitment, setting, organisation, flexibility, FU, outcome, analysis**
- ◆ **Reduce burden of trial specific tasks**
- ◆ **Report well**



References

Perspective

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?
 Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

1. <https://www.precis-2.org/>
2. <http://www.consort-statement.org/extensions?ContentWidgetId=556>
3. www.comet-initiative.org
4. www.ichom.org
5. Zuidegeest M, Goetz I, Groenwold R, et al. Pragmatic trials and real world evidence – an introduction to the series. [J Clin Epidemiol. 2017 Aug;88:7-13](#)
6. Worsley SD, Oude Rengerink K, Irving E, et al. Series: Pragmatic trials and real world evidence: Paper 2. Setting, sites, and investigator selection. [J Clin Epidemiol. 2017 Aug;88:14-20](#)
7. Oude Rengerink K, Kalkman S, Collier, et al. Series: Pragmatic trials and real world evidence: Paper 3. Patient selection challenges and consequences. [J Clin Epidemiol. 2017 Sep;89:173-180](#)
8. Kalkman S, van Thiel GJMW, Zuidegeest MGP et al. Series: Pragmatic trials and real world evidence: Paper 4. Informed consent. [J Clin Epidemiol. 2017 Sep;89:181-187](#)
9. Zuidegeest MGP, Welsing PMJ, van Thiel GJMW et al. Series: Pragmatic trials and real world evidence: Paper 5. Usual care and real life comparators. [J Clin Epidemiol. 2017 Oct;90:92-98](#)
10. Welsing P, Oude Rengerink K, Collier S, et al. Series: Pragmatic trials and real world evidence: Paper 6. Outcome measures in the real world. [J Clin Epidemiol. 2017 Oct;90:99-107](#)
11. Irving E, van den Bor R, Welsing et al. Series: Pragmatic trials and real world evidence: Paper 7. Safety, quality and monitoring. [J Clin Epidemiol. 2017 Nov;91:6-12](#)
12. Meinecke AK, Welsing P, Kafatos G et al. Series: Pragmatic trials and real world evidence: Paper 8. Data collection and management. [J Clin Epidemiol. 2017 Nov;91:13-22](#)
13. Ford I, Norrie, J. Pragmatic trials. [N Engl J Med 2016;375:454-63](#)
14. Giraudeau B, Caille A, Eldridge S et al. Heterogeneity in pragmatic randomised trials: sources and management. [BMC Medicine 2022; 20:372](#)



