Pragmatic Trials

Practice-oriented real-world evidence
Trials: why? How?

- Improve health outcomes through innovation
  - Development: phase I, II, III
  - explanatory
- Inform clinical decision making, evidence-based practice
  - Embedded in clinical practice, real-world
  - Pragmatic
Definitions pragmatic trials

  - 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

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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.


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

Santini V1,2, Allione R2,3, Zini G2,4, Giobia D2, Lunghi M2,5, Poloni A2,6, Giloni D2,7, Sanna A2,8, Masera E2, Ceccarelli M2,3, Abdel-Wahab O2,10, Terenzi A2,11, Angelucci E2,12, Finelli F2,13, Orfida F2,14, Pelzari AM2,15, Ferrero D2,16, Saglio G2,17, Fiqueroa M18, Levi 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

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

van Vliet EO^1, Nimran TA^1, Schuit E^2, Heida KV^1, Opmeer BC^3, Kok M^4, Gyoolaers W^5, Porath MM^6, Woiski M^7, Bax CJ^8, Bloemenkamp KW^9, Scheepers HC^10, Jacquemyn V^11, van Beek E^12, Duvekot JJ^13, Franse R^14, Papatonis DN^15, Kok JH^16, van der Post JA^4, Franx A^1, Mol BW^17, Oudijk MA^18.

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^9, Mulder J^1, Smits-Engelsman BC^4, Ostelo RW^2,5, Oostendorp RAB^1,6, van Tulder MW^2.

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.


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.

# Pragmatic trials

<table>
<thead>
<tr>
<th>Explanatory</th>
<th>Pragmatic</th>
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<tbody>
<tr>
<td>Highly selected participants</td>
<td>Representative participants</td>
</tr>
<tr>
<td>Intervention requires additional resources</td>
<td>Interventions slotted into usual care</td>
</tr>
<tr>
<td>Very standardised delivery, highly controlled adherence</td>
<td>Flexibility in delivery and adherence</td>
</tr>
<tr>
<td>More extensive follow-up</td>
<td>Follow-up = usual care</td>
</tr>
<tr>
<td>Primary outcome not relevant to participants</td>
<td>Primary outcome relevant to participants</td>
</tr>
</tbody>
</table>

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Pragmatic trials

- ‘continuum rather than a dichotomy between explanatory and pragmatic trials’

- ‘pragmatism as an attitude to trial design rather than a characteristic of the trial itself’
Examples

- Routine prescription of medication
- No drug count, minimal evaluation of adherence
- Surgical procedures as done in usual care
- Comparator arm “usual practice”, no placebo
Pragmatic trials

- Pragmatic is not synonym to “easy to conduct” or “sloppy” !!!!
  - Data quality
  - Consent
  - Regulatory
  - Safety
  - Timelines
Eligibility criteria

- 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, 25.42.9). Compared with IMPROVE-IT patients, PINNACLE patients were significantly older, more likely female, had mai

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 criteria

- Do not copy-paste!
- Patients in trial should be representative for target group of intervention
- Broad eligibility criteria (e.g. no selection on trial specific procedures such as expected compliance, language)
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 & training!
- Site initiation and (financial) support
Patient-centred outcomes

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

- **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!
Outcomes

Considerations

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

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

- In pragmatic trials, outcomes should be measured including extraneous effects
  - co-medication,
  - non-adherence
  - placebo effects
  - ...

www.kce.fgov.be
Outcomes

- Observer bias: consider blinded outcome assessment, objective outcomes
- Intention-to-treat analysis
  - Per-protocol if non-inferiority design
- Missing data: importance of feasibility study
Outcomes

Core outcome sets

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

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

**Search COMET database**

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

Enter Keyword [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.
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**

<table>
<thead>
<tr>
<th>Condition Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>21</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>2</td>
</tr>
<tr>
<td>Digestive</td>
<td>1</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>5</td>
</tr>
<tr>
<td>Maternal and neonatal</td>
<td>1</td>
</tr>
<tr>
<td>Mental and behavioral disorders</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>2</td>
</tr>
<tr>
<td>Neurological</td>
<td>2</td>
</tr>
<tr>
<td>Primary/preventative care</td>
<td>1</td>
</tr>
<tr>
<td>Sense organ</td>
<td>2</td>
</tr>
<tr>
<td>Urogenital</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Kenneth F Schulz, Douglas G Altman, David Moher, 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, Shaun Treweek, Joel J Gagnier, Douglas G Altman, Sean Tunis, Brian Haynes, Andrew D Oxman, David Moher, 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.
<table>
<thead>
<tr>
<th>Section</th>
<th>Item</th>
<th>Standard CONSORT description</th>
<th>Extension for pragmatic trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1</td>
<td>How participants were allocated to interventions (eg, “random allocation,” “randomised,” or “randomly assigned”)</td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Methods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>3</td>
<td>Eligibility criteria for participants; settings and locations where the data were collected</td>
<td>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)</td>
</tr>
<tr>
<td>Interventions</td>
<td>4</td>
<td>Precise details of the interventions intended for each group and how and when they were actually administered</td>
<td>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</td>
</tr>
<tr>
<td>Objectives</td>
<td>5</td>
<td>Specific objectives and hypotheses</td>
<td>Describe the comparator in similar detail to the intervention</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6</td>
<td>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)</td>
<td>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</td>
</tr>
<tr>
<td>Sample size</td>
<td>7</td>
<td>How sample size was determined; explanation of any interim analyses and stopping rules when applicable</td>
<td>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</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>11</td>
<td>Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment</td>
<td>If blinding was not done, or was not possible, explain why</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>Statistical methods used to compare groups for primary outcomes; methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Participant flow</td>
<td>13</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>
Take home messages

- Pragmatic trial: benefit/harm in routine clinical practice
- Approach to trial design: eligibility, recruitment, setting, organisation, flexibility, FU, outcome, analysis
- Make your trial relevant for real-world practice
- Reduce burden of trial specific tasks
- Report well
References

3. www.comet-initiative.org
4. www.ichom.org
THANK YOU!

http://ikce.yourict.net/?q=node/1957