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How did they do that?

Replicating Clinical Trial Interventions In Clinical Practice

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Session Educational Objectives



1. List features or elements of an effective description of a research intervention
2. Given a medical journal article describing a research intervention, identify and summarize deficiencies that would make it difficult to apply the intervention in clinical practice
3. Generate feedback to the author(s) and journal editors that communicates clearly what additional information is needed to apply the intervention in practice.

Agenda



- Introduction: Dr. Clark
(5 minutes)
- Background: Dr. Loder
(15 minutes)
- Small group article reviews
(30 minutes)
- Review and discussion of results
(30 minutes)
- Conclusion and Evaluations
(5 minutes each)

The Problem



- Translation of evidence into practice is slow
- Reasons? Clinicians may be
 - Unaware of results
 - Perceive results as invalid or inapplicable to their patients
 - Forget to use the treatment

Dopson S, Locock L, Chambers D, Gabbay J. Implementation of evidence-based medicine: evaluation of the Promoting Action on Clinical Effectiveness programme. *Journal of Health Serv Res Policy* 2006;6:23-31.

Pathman DE, Konrad TR, Freed GL, Freeman VA, Koch GG. The awareness-to-adherence model of the steps to clinical guideline compliance. The case of pediatric vaccine recommendations. *Med Care*. 1996 Sep;34(9):873-89.

Glasziou P, Haynes B. The paths from research to improved health outcomes. *ACP J Club*. 2005 Mar-Apr;142(2):A8-10.

The Problem



- One important reason might be clinician inability to carry out the treatment based on published information

Glasziou P, Haynes B. The paths from research to improved health outcomes. *ACP J Club*. 2005 Mar-Apr;142(2):A8-10.

Efforts to improve trial reporting



- CONSORT (Consolidated Standards of Reporting Trials)
- Guidelines largely aim at matters that affect internal validity

Moher D, Schulz KF, Altman D; CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *JAMA*. 2001;285(15): 1987-1991.

What about translation?



- RCT interventions are often complex
- Reports may omit information about the implementation of interventions
- In the real world
 - Practitioners may not deliver them in the same way
 - Participants may not behave in the same way
 - The context/system may be different

Mayo-Wilson E.. Reporting implementation in randomized trials: proposed additions to the consolidated standards of reporting trials statement. Am J Public Health. 2007 Apr;97(4):630-3

Glasgow RE, Emmons KM. How can we increase translation of research into practice? Types of evidence needed. Annu Rev Public Health. 2007;28:413-33

Proposed standards



“Particularly for complex interventions, the CONSORT statement does not include all types of information needed to understand the results of randomized controlled trials. CONSORT should be expanded to include more information about the implementation of interventions in all trial arms”

Mayo-Wilson E.. Reporting implementation in randomized trials: proposed additions to the consolidated standards of reporting trials statement. Am J Public Health. 2007 Apr;97(4):630-3

It's a fair point...Example # 1



- A survey of 80 studies selected for abstraction in Evidence-Based Medicine 10/2005-20/2006
- Two GPs asked "Could you use this treatment with a patient if you saw them tomorrow?"

Glasziou, P. Oral Presentation, International Clinical Trials Symposium, Sydney, Australia

It's a fair point...Example # 1



- Missing elements in 41/80 (51%)
 - Information better for control interventions (often placebo)
 - Better for drug than non-drug information
- What was missing
 - Description of process
 - Handouts or booklets or sources
 - Patient instructions
 - Description of equipment

Example # 2



- A case-control study of hyperkalemia in 523 patients receiving an angiotensin converting enzyme inhibitor who were hospitalized for hyperkalemia
- 8.2% of cases had been using a potassium-sparing diuretic, in contrast to only 0.3% of 25 807 controls.
- The adjusted odds ratio was 20.3 (95% confidence interval, 13.4 to 38.7).

Example # 2



- Contrast this with a randomized trial in patients with congestive heart failure treated with an angiotensin-converting enzyme inhibitor
- This showed almost no difference in the incidence of severe hyperkalemia between patients assigned to receive a potassium-sparing diuretic (spironolactone) and those assigned to receive placebo.

How can this be?



- Commentators have pointed to the “monitoring for safety that occurred in patients enrolled in the randomized trial.
- A low starting dose, frequent repeated measurement of serum potassium levels
- “This cautious approach to administering spironolactone, just as much a part of the intervention as the specific drugs administered to study participants, probably differed from the approach of some physicians who provided care to patients in the community setting in which the case-control study was conducted.”

What's part of the intervention?



- Many things we may not think of
 - “Nursing dose”
 - Patient characteristics
 - Nature of treatment protocol
 - Conditions of practice
 - Duration of treatment and followup
 - Adherence
 - Exclusion criteria

Reed D et al. Measuring the dose of nursing intervention. *Int J Nurs Terminol Classif.* 2007 Oct-Dec;18(4):121-30.

Ujeen AA, et al, Hypertension patients participating in trials differ in many aspects from patients treated in general practices.

BMJ/Oxford Initiative



- The BMJ is engaged in a prospective study of RCTs with the Center for Evidence Based Medicine at Oxford.
- Authors of BMJ articles are asked to provide additional useful information to be published alongside their papers on bmj.com.
- The research will evaluate researchers' estimates of the replicability of the interventions before and after the provision of this additional information.

BMJ/Oxford Initiative



- What's missing?
- The perspective of practicing clinicians
- That's where you come in!

Problems

- Not practical to do RCTs in every population and subgroup
- Yet results of trials have to be generalized
- How can journals report trials in a way that facilitates this?

Problems

- For pharmacological treatments the description might include the dose, titration, route, timing, duration, and any monitoring used.
- For complex treatments it's even trickier.

Are checklists the answer?

- Information about “who, what, when, and where” of the treatment is desirable but differs for interventions
- Full treatment descriptions should include
 - any procedures used
 - the timing of treatment including duration and intervals of dosing
 - materials needed (such as patient handouts or devices)
 - accessibility of any materials or instructions, including current language.
 - Supplementation with graphical methods of description and copies of materials or handouts
 - Electronic publishing of extra material?

Group 1



- Group 1 will consider an accepted BMJ article that is not yet published (authors have agreed to this).
- Participants will prepare feedback to the authors of the article.
- From the point of view of their practice and their patients, participants will
 - 1) Identify useful features of the intervention description
 - 2) Identify information barriers to implementing the intervention in practice
 - 3) Prepare a list of suggested improvements for the authors

Group 2



- Group 2 will consider this published article with extra description of the intervention:

Effectiveness and safety of chest pain assessment to prevent emergency admissions: ESCAPE cluster randomised trial. Steve Goodacre et al. *BMJ* 2007;335:659, doi:10.1136/bmj.39325.624109.

- Participants will then

- 1) Complete the BMJ/Oxford survey about the adequacy of the intervention description
- 2) Tell us what's still missing!

Discussion of Group Results



- Working together, and based on the summary of results from each group participants will devise an ideal “reader’s checklist” of the practical information they need to translate trial-described interventions into clinical practice.

Can such feedback change reporting practices?

- The author of a randomized trial of graded exercise for chronic fatigue syndrome received many requests for further information about the exercise program
- This led to a supplementary article with a more detailed “prescription”
- “Similarly it is not possible to implement a stroke unit, low fat diets, or smoking cessation advice without sufficient details on the components that were planned and delivered”

Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust.* 2004;180(9):444-8.

Wallman KE, Morton AR, Goodman C, Grove R. Exercise prescription for individuals with chronic fatigue syndrome. *Med J Aust.* 2005 Aug 1;183(3):142-3

Mayo-Wilson E. Reporting implementation in randomized trials: proposed additions to the consolidated standards of reporting trials statement. *Am J Public Health.* 2007 Apr;97(4):630-3.