

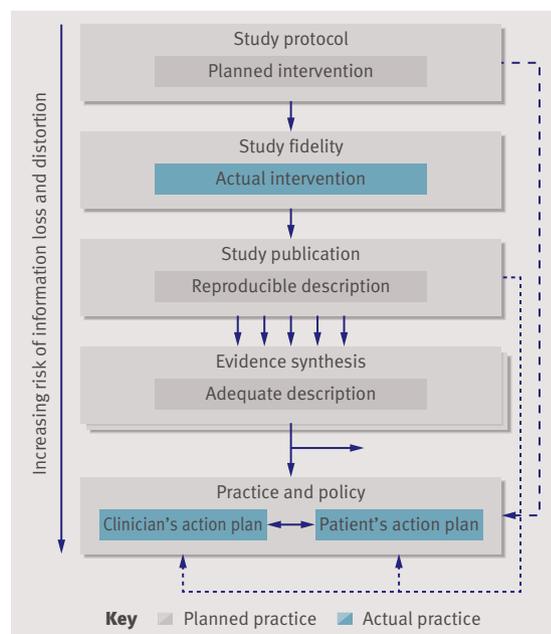
# RESEARCH METHODS & REPORTING

## Taking healthcare interventions from trial to practice

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The results of thousands of trials are never acted on because their published reports do not describe the interventions in enough detail. How can we improve the reporting?

Much healthcare research is currently wasted because its findings are unusable.<sup>1</sup> Published reports of intervention trials often focus on the results and fail to describe interventions adequately. For example, a review of 80 studies selected for the journal *Evidence Based Medicine* as both valid and important for clinical practice found that clinicians could replicate the intervention in only half the studies.<sup>2</sup> Interventions may be used incorrectly or not at all if there is inadequate detail in the trial protocol, on the conduct of the trial, in systematic reviews and guidelines, and finally during implementation (fig 1). This is an unnecessary but remediable waste, as we discuss below.



**Fig 1** | Distortion or loss of information about the true intervention can occur at each of four stages and the intervention may not reach practice without good reporting and trial fidelity (shaded boxes)

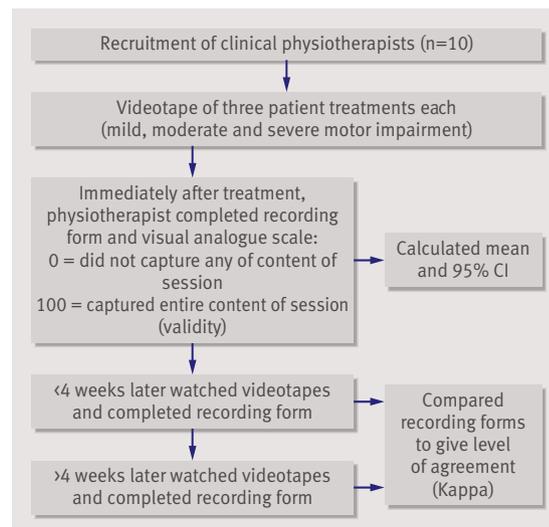
### Study protocol

The methods section in a protocol should provide a description of the intervention(s) (whether active, usual practice, or placebo) that is sufficiently detailed to enable people with appropriate expertise to reproduce them. This should include:

- What were the “contents,” including all constituent components, materials, and resources and their quality
- Who delivered the intervention, including their expertise, additional training, and support
- Where the intervention was delivered (the setting)
- How and when the intervention was delivered: the dose, the schedule (intensity, frequency, duration), and interaction
- The degree of flexibility permissible, including options and decision points.<sup>3</sup>

This list is readily adaptable for interventions beyond clinical treatments and encounters—for example, to health systems and other complex interventions. Attention should be paid to the different meanings that terms such as counselling or physical therapy may have in different settings.

Space constraints in trial registration databases and



**Fig 2** | Illustration of methods to develop a physical therapy treatment schedule<sup>5</sup>

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### Summary of studies that assessed whether interventions in published trial reports could be replicated

Clinical area	No of Trials	No (%) replicable	Methods of assessment
Back pain <sup>12</sup>	24	3 (13)	Information sufficient for consumers
Surgical procedures <sup>13</sup>	158	138 (87)	Required only that "some" detail was provided, not sufficient for replication; 41% also provided some detail on actual surgery used
Weight loss interventions <sup>14</sup>	63	62 (98)	Compliance with item 4 of CONSORT statement*
Range of topics published in <i>Evidence Based Medicine</i> <sup>2</sup>	55	36 (65)	Two general practitioners were independently asked whether they could use this treatment with patients if they saw them tomorrow

\*2001 update.<sup>11</sup>

scientific journals may restrict full reporting of interventions. Potential solutions include complying with WHO requirements for reporting interventions, adding web hyperlinks to trial registration records and other documentation,<sup>4</sup> as recommended by signatories to the Ottawa statement ([ottawagroup.ohri.ca](http://ottawagroup.ohri.ca)) and on other websites where protocols are reported.

The development and description of treatment schedules may take considerable planning, particularly for non-drug interventions. Figure 2 shows the development of conventional physical therapy interventions as a precursor to studies evaluating novel interventions for recovery of movement after stroke.<sup>5</sup> Semistructured interviews and focus groups were used to capture the content of conventional physical therapy interventions.<sup>5</sup>

#### Study fidelity: planned versus actual treatment

Trial reports should describe the extent to which the intervention, as delivered, was consistent with the protocol. Fidelity can have several dimensions: whether components are delivered as prescribed (adherence); the amount of exposure to the content; the extent to which the delivery was aligned with the underpinning theory (quality); and the degree to which participants engaged in<sup>6</sup> or modified the intervention. Poor fidelity will lead to unclear or misleading conclusions.

Despite its importance, fidelity of the intervention is often not reported: only 25 of 80 (31%) prevention studies reported evidence of fidelity,<sup>6</sup> and only 69 of 192 (36%) drug studies documented assessment of adherence to treatment—the simplest measure of fidelity.<sup>7</sup>

Assessment of fidelity may require qualitative and quantitative methods. For example, a trial comparing the effect of two diagnostic tests for malaria delivered inconclusive results, but a parallel qualitative study showed that in areas of high malaria prevalence clinicians treated malaria regardless of the random allocation.<sup>8</sup> Likewise, in a large trial of an intervention to increase physical activity in sedentary adults, coding of session audiotapes showed that only 42% of intervention techniques were delivered as specified in the protocol.<sup>9</sup>

Interventions can involve several actors. Though clinicians may deliver the intervention, participants may not adhere to it. Hence the role of both clinician and participant needs to be described. An example of good practice is the DiGEM trial of self monitoring of blood glucose concentrations,<sup>10</sup> for which the nurse training manual describes the intervention and timing of delivery in detail, with the intended effect and the required level of knowledge, skills, and behaviour for the research nurse and the person with diabetes.

Measures to improve and assess fidelity at the trial protocol stage include:

- Designing the intervention using a recognised theoretical framework
- Producing a manual or written instructions for the interventions
- Training all study members responsible for protocol delivery
- Observing delivery
- Using checklists to ensure competency and standardisation of delivery
- Providing support material for trial participants that promotes adherence.

Any drift away from fidelity during the trial should be reported when the study is published.

#### Publication of single studies

The Uniform Requirements for Manuscripts Submitted to Biomedical Journals have for many years advised authors to "Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results" ([www.icmje.org](http://www.icmje.org)).

It is unclear why this suggestion has not been extended to all aspects of the research methods. The need to provide detailed information about interventions has been recognised in several guidelines for reporting research, the best known of which is the CONSORT (Consolidated Standards of Reporting Trials) statement.<sup>11</sup> And the 2010 update of the CONSORT statement requires authors to describe "the interventions for each group with sufficient details to allow replication, including how and when they were actually administered."

Despite the CONSORT guidelines and advice on good reporting of interventions, reporting is currently poor (table). For example, only 13% of papers on back pain reported reproducible interventions.<sup>12</sup> A review of 158 reports of randomised controlled trials in surgery showed that important components of the intervention (such as anaesthesia protocol or perioperative management) were reported in less than half.<sup>13</sup> Furthermore, only 41% reported the intervention actually administered as opposed to the intervention intended in the protocol.<sup>13</sup>

Since 2001, extensions to CONSORT have focused on specific types of intervention with detailed recommendations on reporting interventions. For example, the extension to trials of non-drug treatments<sup>15</sup> recommended the reporting of precise details of both the experimental treatment and comparator, including a description of the different components of the interventions and, when applicable, descriptions of the procedure for tailoring the interventions to individual participants; details of how the interventions were standardised, and details of how adherence to the protocol of care providers was assessed or enhanced. The extensions for other types of study have not directly tackled ability to replicate interventions, although the WIDER (Workgroup for Intervention Development and Evaluation Research) group of journal editors has given recommendations to ensure behavioural interventions can be replicated.<sup>16</sup>

Adequate reporting is difficult and needs greater attention from authors, peer reviewers, and journals. Trials of complex interventions particularly may benefit from

innovative communication methods such as graphic techniques,<sup>17</sup> video, and audio. For example, videos are available to guide use of the WHO safe surgery checklist.<sup>18</sup>

### Synthesis of evidence and systematic reviews

Interventions will usually vary across trials in a systematic review, reflecting differing inclusion criteria and specific aspects of the intervention. Even for relatively simple interventions, such as antibiotics for acute sinusitis, the specific antibiotic, dose, duration, and timing may vary. For more complex interventions, such as strategies to implement clinical practice guidelines, heterogeneity is greater.<sup>19</sup>

For the reviewer user a central question is: “Which intervention should we use when there are multiple versions in a review?” For example, a review reported that exercise for patients with osteoarthritis of the knee can reduce pain and improve function.<sup>20</sup> However, almost all studies in the review used different types and doses of exercise. If a review shows a collective intervention to be effective, the user is challenged to determine which configuration, elements, or dose of the intervention should be implemented for their patients or setting. Methods to guide this are poorly developed. (Note: identical problems occur in guideline development.)

During synthesis of evidence, the intervention description may be modified at several stages:

*The review protocol*—An intervention may be inadequately conceptualised at the protocol stage

*Conducting the review*—Authors may not consider the features of an intervention that could affect implementation and instead focus on classifying interventions for exploring heterogeneity

*Dissemination*—When the review enters the media, the description of the intervention may be altered

This complicates decisions about which configuration of the intervention to implement.

With rare exceptions<sup>21</sup> reviewers seldom attempt to improve descriptions of interventions. Conceptual frameworks may facilitate the classification and description of interventions. For example, a review of “audit and feedback” classified interventions according to intensity and provided examples to illustrate different intensities.<sup>22</sup> This categorisation was intuitive and not based on theory. Using theory may lead to conceptually more coherent categories and therefore more meaningful results.

### Mapping the components of an intervention

Specifying the components within interventions in a review can help identify similarities and differences, allowing the effective “ingredients” to be defined. For example, Rubenstein used cross-case qualitative analysis to assess whether specific design features of collaborative care interventions were associated with greater effect on depression compared with usual care.<sup>23</sup> This qualitative analysis looked closely at features that occurred in studies with greater effects, generating hypotheses about the most important components of the intervention. Core components may also be identified by surveying trialists. For example, Langhorne et al used all trials of “stroke units” to identify key components then surveyed the trialists’ collaboration to find out which components they had used and derive a composite intervention.<sup>21</sup>

### Actions to improve usefulness of research reports

- When planning trials, researchers should work with end users to develop and deliver the interventions. Clear specifications of the components of the intervention should be planned and reported
- Researchers and funders should improve the description of interventions (including “usual practice”) in protocols and pay attention to the fidelity of an intervention
- A stable “intervention bank” should be established (eg, videos, manuals, and fidelity tools linked to trial registration number) to overcome the problem of word restrictions in journals, etc
- Systematic reviews should include a summary table describing study interventions, with links to trial publications and other resources relevant to replicating the interventions
- The reporting standards for interventions in trials (CONSORT, etc) and systematic reviews (PRISMA<sup>26</sup>) should be improved and standardised (specific checklists)

### Taxonomies

One method of identifying the active ingredient(s) of an intervention is to systematically specify them—and control comparison conditions—using standardised taxonomies and then use meta-regression to show effects hidden by more conventional methods of synthesising evidence.<sup>24 25</sup> Taxonomies help ensure a planned approach to analysis, particularly when heterogeneity prevents meta-analysis. Taxonomies facilitate the process of accumulating knowledge across heterogeneous studies, making it easier to update reviews and identify gaps. Mechanisms underlying an intervention can be investigated by linking active ingredients to hypothesised causal mechanisms (theory) through approaches such as “realist synthesis” or consensus among content experts.

### Using the study

Unless there is clarity about what interventions involve, patients and health professionals cannot ensure they receive beneficial interventions or avoid unhelpful or harmful interventions.

Patients, practitioners, and policy makers learn about interventions directly from trials and systematic reviews or, more commonly, from intermediaries and secondary sources (websites, advice centres, media, clinical practice guidelines, librarians) or practitioners. The details of evaluated interventions should be readily available in the public domain. The minimal elements of knowledge that patients (or the providers of information to patients) need about the intervention are who, what, when, and how, as we set out above. Additionally, clinicians may need information about skills, equipment, or referral sources to provide effective treatment. The box gives our proposals to increase the usefulness of research reports (box).

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- Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009;374:86-9.
- Glasziou P, Meats E, Heneghan C, Shepperd S. What is missing from descriptions of treatment in trials and reviews? *BMJ* 2008;336:1472-4.
- Lustria ML, Cortese J, Noar SM, Glueckauf RL. Computer tailored health interventions delivered over the web: review and analysis of key components. *Patient Educ Counsel* 2009;74:156-73.
- Chan A-W. Bias, spin, and misreporting: time for full access to trial protocols and results. *PLoS Med* 2008;5:e230.
- Pomeroy VM, Cooke E, Hamilton S, Whittet A, Tallis RC. Development of a schedule of current physiotherapy treatment used to improve movement control and functional use of the lower limb after stroke: a precursor to a clinical trial. *Neurorehabil Neural Repair* 2005;19:350-9.
- Dane AV, Schneider BH. Program integrity in primary and early secondary prevention: are implementation effects out of control? *Clin Psychol Rev* 1998;18:23-45.
- Gossec L, Tubach F, Dougados M, Ravaud P. Reporting of adherence to medication in recent randomized controlled trials of 6 chronic diseases: a systematic literature review. *Am J Med Sci* 2007;334:248-54.
- Lubell Y, Reyburn H, Mbakiliwa H, Mwangi R, Chonya S, Whitty CJ, et al. The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. *BMJ* 2008;336:202-5.
- Hardeman W, Michie S, Fanshawe T, Prevost AT, McLoughlin K, Kinmonth AL. Fidelity of delivery of a physical activity intervention: Predictors and consequences. *Psychol Health* 2008;23:11-24.
- Farmer A, Wade A, French D, Simon J, Yudkin P, Gray A, et al. Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial. *Health Technol Assess* 2009;13:1-72.
- Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Intern Med* 2001;134:657-62.
- Glenton C, Underland V, Kho M, Pennick V, Oxman AD. Summaries of findings, descriptions of treatments, and information about adverse effects would make reviews more informative. *J Clin Epidemiol* 2006;59:770-8.
- Jacquier I, Boutron I, Moher D, Roy C, Ravaud P. The reporting of randomized clinical trials using a surgical intervention is in need of immediate improvement: a systematic review. *Ann Surg* 2006;244:677-83.
- Thabane L, Chu R, Cuddy K, Douketis J. What is the quality of reporting in weight loss intervention studies? A systematic review of randomized controlled trials. *Int J Obes (Lond)* 2007.
- Boutron I, Moher D, Altman DG, Schulz K, Ravaud P, for the CONSORT group. Methods and processes of the CONSORT group: example of an extension for trials assessing nonpharmacologic treatments. *Ann Intern Med* 2008;W60-W67.
- Workgroup for Intervention Development and Evaluation Research. WIDER recommendations to improve reporting of the content of behaviour change interventions. 2009. <http://interventiondesign.co.uk/wp-content/uploads/2009/02/wider-recommendations.pdf>.
- Perera R, Heneghan C, Yudkin P. Graphical method for depicting randomised trials of complex interventions. *BMJ* 2007;334:127-9.
- WHO Safe Surgery Checklist. Instructional videos. [www.who.int/patientsafety/safesurgery/tools\\_resources/en/index.html](http://www.who.int/patientsafety/safesurgery/tools_resources/en/index.html).
- Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;337:a1655.
- Fransen M, McConnell S. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2008;4:CD004376.
- Langhorne P, Pollock A, with the Stroke Unit Trialists Collaboration. What are the components of effective stroke unit care? *Age Ageing* 2002;31:365-71.
- Jamtvedt G, Young JM, Kristoffersen DT, O'Brien MA, Oxman AD. Audit and feedback: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2006;2:CD002259.
- Rubenstein LV, Williams Jr JW, Danz M, Shekelle P. Evidence synthesis for determining the key features of effective depression interventions. 2009. [www.hsrd.research.va.gov/publications/esp/#depression](http://www.hsrd.research.va.gov/publications/esp/#depression).
- Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. *Health Psychol* 2008;27:379-87.
- Michie S, Abraham C. Advancing the science of behaviour change: a plea for scientific reporting. *Addiction* 2008;103:1409-10.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.

## ANSWERS TO ENDGAMES, p 407. For long answers go to the Education channel on [bmj.com](http://bmj.com)

### CASE REPORT

#### An "unforeseen" complication of urinary tract infection in a patient with diabetes

- A preliminary diagnosis of endogenous endophthalmitis secondary to urinary tract infection and complicated by pneumonia was made. The superior choroidal swelling seen on the B-scan ocular ultrasound is probably an echogenic choroidal or subretinal mass representing a choroidal abscess.
- Gram negative bacteria, especially *Klebsiella pneumoniae*, are common causative agents in east Asia, whereas Gram positive bacteria are more prevalent in other settings. Other organisms less commonly involved in endogenous endophthalmitis include fungi (in particular *Candida* spp and *Aspergillus* spp), mycobacteria, and parasites (for example, *Toxoplasma gondii*).
- In bacterial endogenous endophthalmitis, blood culture gives the highest diagnostic yield (72%), followed by analysis of ocular fluid (36-73%). In fungal endogenous endophthalmitis, blood cultures are almost always negative but vitreous cultures are usually positive. In view of the difficulty in differentiating between bacterial and fungal endogenous endophthalmitis at presentation, blood culture should always be included in the septic workup.
- Investigations to determine the source of infection should be undertaken. These include echocardiogram (for infective endocarditis) and imaging of the abdomen (for liver abscess and other intra-abdominal infective foci).
- Broad spectrum intravenous antibiotics and possibly intravitreal antibiotics should be initiated immediately.

### STATISTICAL QUESTION

#### Odds ratios

Answers b, c, and d are true, whereas a is false.

### ON EXAMINATION QUIZ

#### Hypertrophic cardiomyopathy

Answer E is the correct answer.

### ANATOMY QUIZ

#### Magnetic resonance image of the left ankle

- Tibialis posterior tendon
- Flexor digitorum longus tendon
- Flexor hallucis longus tendon
- Fibula
- Peroneus longus tendon