How to build a syllabus to ensure responsible, reproducible research

EBHC preconference workshop Sicily, October 2017

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Competing interests

I'm editor in chief of BMJ Open and Director of academic outreach at BMJ Publishing Group, owned by the British Medical Association (BMA)

Part of the revenue for BMJ comes from drug & device manufacturers through advertising, reprint sales, & sponsorship. The BMJ (British Medical Journal) and BMJ Open are open access journals that charge article publishing fees for research. I'm editorial lead for the BMJ Research to Publication eLearning programme (by subscription).

My annual bonus scheme is based partly on the overall financial performance of both BMJ and BMJ Research to Publication.

The scandal of poor medical research

...”What...should we think about researchers who use the wrong techniques (either wilfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions?

We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common. [1-7] This is surely a scandal.”

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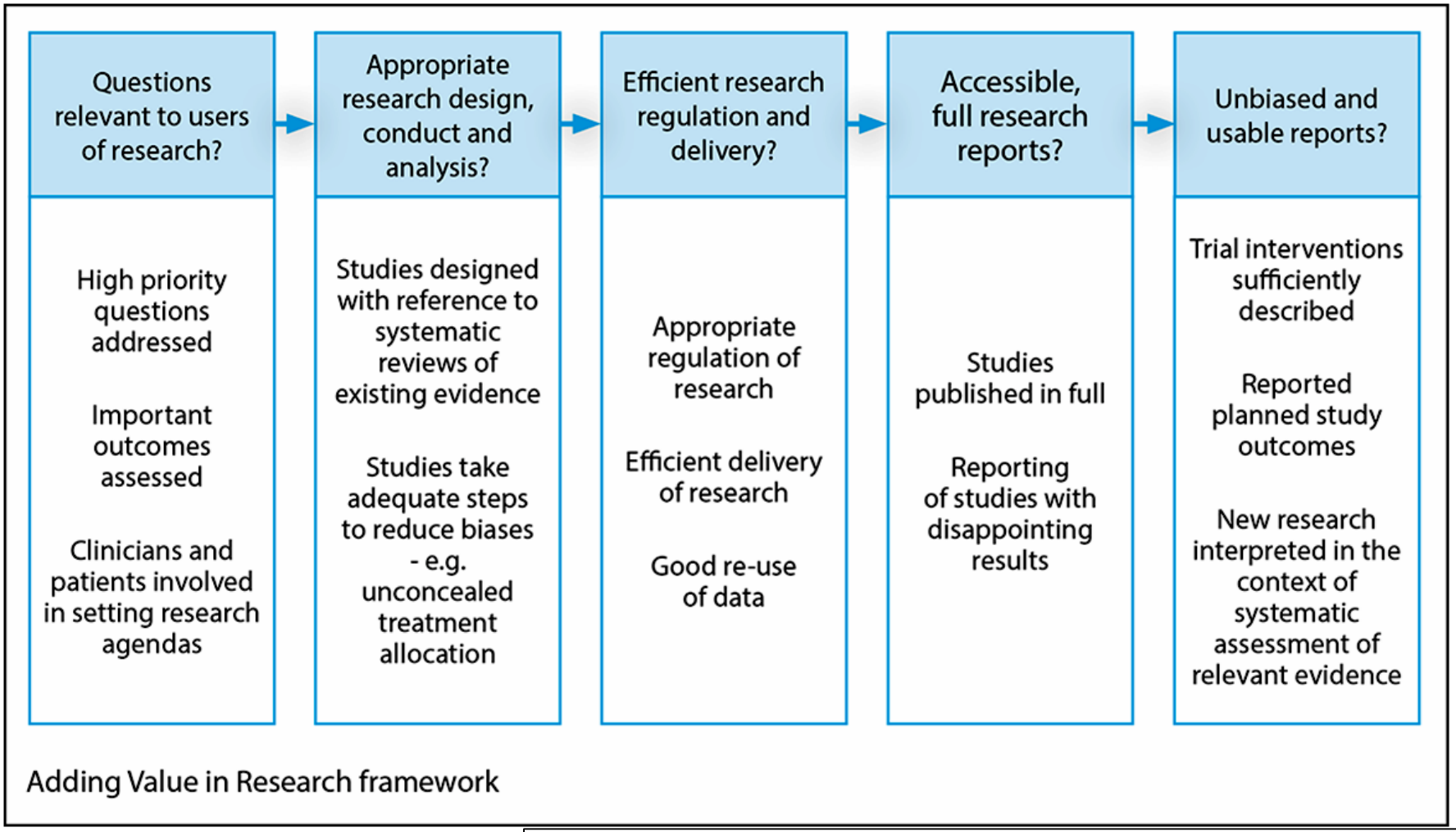
Altman D G. The scandal of poor medical research. BMJ 1994; 308 :283

We need less research, better research, and research done for the right reasons

85% research wasted, costing >$100bn/yr



Adding Value in Research framework

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Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet 2014; 374: 86-9.

Let's increase research value and reduce harm

- review identified reporting bias in 40 indications comprising around 50 pharmacological, surgical (e.g. vacuum-assisted closure therapy), diagnostic (e.g. ultrasound), and preventive (e.g. cancer vaccines) interventions
- many cases involved withholding of study data by manufacturers and regulatory agencies or active attempts by manufacturers to suppress publication
- reporting bias can overestimate efficacy and underestimate safety risks of interventions

thebmj

McGauran, N, Wieseler, B, Kreis, J, Schüler, YB, Kölsch, H, and Kaiser, T. Reporting bias in medical research—a narrative review. Trials. 2010; **11**: 37

Underestimation of benefit can be wasteful too

- data from published systematic reviews and meta-analyses and unpublished FDA reviews were used in revised meta-analyses for 9 drugs approved by U.S. FDA in 2001-2

- summary estimate of the single harm outcome found greater harm after inclusion of unpublished FDA trial data

- addition of unpublished FDA trial data caused 46% (19/41) of summary estimates to show lower drug efficacy, 7% (3/41) to show identical efficacy, 46% (19/41) to show greater efficacy

thebmj

Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses *BMJ* 2012; 344:d7202

‘Negative’ trials less likely to be published

From meta-analysis by Song et al: pooled odds ratios of publication of studies with positive results, compared to those without positive results (publication bias):

- 2.78 (95% CI: 2.10 to 3.69) in cohorts of studies from inception
- 5.00 (95% CI: 2.01 to 12.45) in trials submitted to regulatory authority
- 1.70 (95% CI: 1.44 to 2.02) in abstract cohorts,
- 1.06 (95% CI: 0.80 to 1.39) in cohorts of manuscripts.

It seems that publication bias occurs mainly before the presentation of findings at conferences and before the submission of manuscript to journals (the “file drawer problem”)

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Song F, Parekh-Bhurke S, Hooper L, Yoke YK, Ryder JJ, Sutton AJ, Hing CB, Harvey I. BMC Medical Research Methodology 2009, **9**:79 doi:10.1186/1471-2288-9-79

Published trials are poorly reported

30 years ago some statisticians looked at 45 reports of comparative trials published in The BMJ, the Lancet, or New England Journal of Medicine and found:

- common failure to specify in advance the intended size of a trial or statistical stopping rules for interim analyses
- summaries or abstracts of trials tended to emphasize the more statistically significant end points
- overall, reporting of clinical trials appeared biased towards exaggerating treatment differences.

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Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. A survey of three medical journals. N Engl J Med 1987;317:426–32.

Core capabilities

- literature searching
- ability to understand systematic reviews
- statistics, methodology
- transparency
- **reproducibility**

Replication: desirable, but not always possible

- scientific evidence strengthened when important findings are replicated by multiple investigators using independent data, analytical methods, laboratories, and instruments
- replication is standard in basic sciences
- time and expense required for epidemiological studies means many are often not fully replicable, so policy decisions must be made with available evidence

Should at least ensure **reproducibility**

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Peng RD, Dominici F, Zeger SL. Reproducible Epidemiologic Research. Am J Epidemiol 2006;163: 783-9 doi:10.1093/aje/kwj093

Reproducibility: should always be possible

- reproducibility is an attainable minimum standard
- independent investigators subject the original data to their own analyses and interpretations
- reproducibility requires datasets and software to be available for:
  - verifying published findings
  - conducting alternative analyses of the same data
  - eliminating uninformed criticisms that do not stand up
  - expediting interchange of ideas among investigators

thebmj

Peng RD, Dominici F, Zeger SL. Reproducible Epidemiologic Research. Am J Epidemiol 2006;163: 783-9 doi:10.1093/aje/kwj093

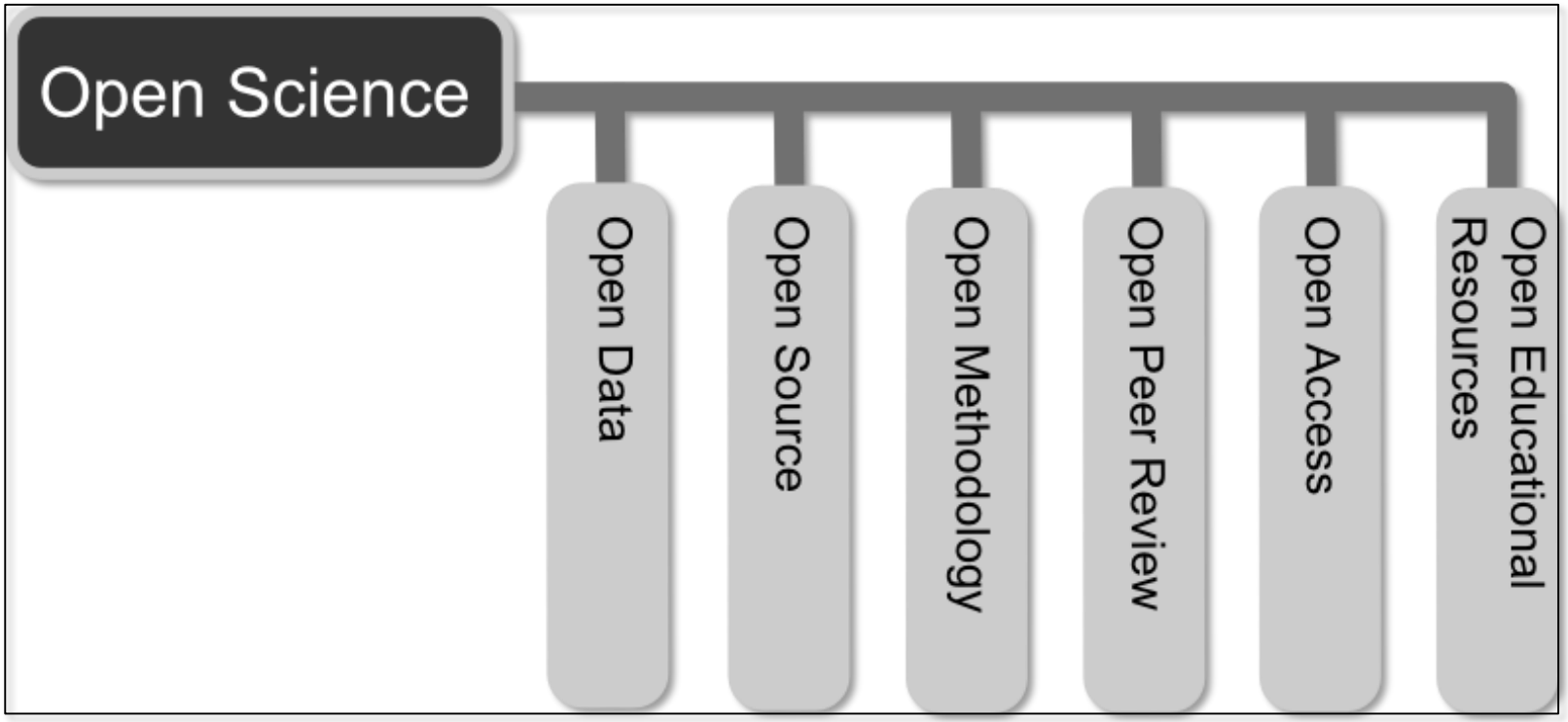
What does reproducibility actually mean?

- methods reproducibility
- results reproducibility (via data, metadata, code)
- robustness and generalisability
- inferential reproducibility
  - hampered by selective reporting, data mining/dredging/torturing, p-hacking, HARKing (hypothesising after results known)

Goodman SN, Fanelli D, Ioannidis JPA. What does research reproducibility mean? Sci Trans Med 2016: 341PS12
http://stm.sciencemag.org/content/8/341/341ps12.full

Open Science

“Open data and content can be freely used, modified, and shared by anyone for any purpose”



Transparent reporting of clinical trials

Trial registry

But providing access to full protocols is voluntary and inconsistent

Zarin DA, Tse T. Medicine. Moving toward transparency of clinical trials. Science 2008 Mar 7;319(5868):1340-2.

COMPARE

TRACKING SWITCHED OUTCOMES IN CLINICAL TRIALS

METHODS | RESULTS | TEAM | BLOG | FAQ

67	9	354	357
TRIALS CHECKED	TRIALS WERE PERFECT	OUTCOMES NOT REPORTED	NEW OUTCOMES SILENTLY ADDED

On average, each trial reported just 58.2% of its specified outcomes. And on average, each trial silently added 5.3 new outcomes.

58	18	8	32
LETTERS SENT	LETTERS PUBLISHED	LETTERS UNPUBLISHED AFTER 4 WEEKS	LETTERS REJECTED BY EDITOR

From Oct 2015 - Jan 2016 the COMPare Trials Project team systematically checked every trial published in NEJM, JAMA, The Lancet, Annals of Internal Medicine, and The BMJ to see if they misreported their findings

http://compare-trials.org

Sharing de-identified individual participant data (IPD) from clinical trials

To maximise fidelity of evidence base ...and:

- allow testing of secondary hypotheses
- aid design of future trials
- simplify data acquisition for IPD meta-analysis
- aid developing/evaluating novel statistical methods
- ensure analyses can be reproduced and checked
- provide incentive to ensure accuracy of dataset
- reduce deliberate misconduct
- whose data are they anyway?

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Vickers AJ. Whose data set is it anyway? Sharing raw data from randomized trials. *Trials* 2006, 7:15doi:10.1186/1745-6215-7-15

Data sharing: regulator and industry initiatives

- EMA is providing public access to clinical study reports

- July 2014 Principles for Responsible Clinical Trial Data Sharing from European Federation of Pharmaceutical Industries and Associations (EFPIA) and Pharmaceutical Research and Manufacturers of America (PhRMA)

- controlled access to online databases of de-identified individual patient data from trials through initiatives such as:
  - https://www.clinicalstudydatarequest.com
  - Yale University Open Data Access (YODA) Project http://yoda.yale.edu/
  - https://www.projectdatasphere.org for cancer trial data

The BMJ's policy: data sharing on request

Mandatory since 2013 for any paper reporting main endpoints of an RCT of one or more drugs or medical devices in current use. Extending 2015 to all trials submitted to The BMJ

Oct 2016: survey in BMJ Open covering 21 clinical trials bound by The BMJ policy reported that only 5/21 had made data sets available.

One data set was freely available on Dryad, leaving 20 RCTs whose authors were emailed to request data:

- 13 did not respond
- 4 made the data available
- 3 declined, citing caveats about the survey

thebmj

Has open data arrived at the *British Medical Journal (BMJ)*? An observational study. Rowhani-Farid A, Barnett AG.
BMJ Open 2016;6:10 e011784 doi:10.1136/bmjopen-2016-011784

ICMJE 2017 policy on sharing clinical trial data

As of 1 July 2018 manuscripts submitted to any ICMJE journal* that report the results of clinical trials must contain a data sharing statement.

Clinical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.

www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

*International Committee of Medical Journal Editors (ICMJE) current journals: *Annals of Internal Medicine*, *The BMJ*, *Deutsches Ärzteblatt*, *Ethiopian Journal of Health Sciences*, *JAMA*, *Journal of Korean Medical Science*, *New England Journal of Medicine*, *New Zealand Medical Journal*, *PLOS Medicine*, *Lancet*, *Revista Médica de Chile*, *Ugeskrift for Laeger* (members in 2016-17)

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ICMJE 2017 policy on data sharing statements

Statements must indicate:

- whether individual deidentified participant data (incl. data dictionaries) will be shared
- what data will be shared
- whether related documents will be available (eg trial protocol, statistical analysis plan)
- when the data will become available and for how long
- access criteria (with whom, for what types of analyses, by what mechanism)

Editors may take data sharing statements into account when making decisions on peer review and acceptance of papers

Patient perspective: more research needed

"Patients expect that health care professionals and researchers use patient data in the best possible way. That there is a fight over what the best way is perplexing and disappointing."

"If you have a life-threatening disease and need help, you do not care much about privacy. The question is also: How many people will die if we don't share data?

Patients cited in NEJM debate April 2017

thebmj

Haug CJ. Whose Data Are They Anyway? Can a Patient Perspective Advance the Data-Sharing Debate? NEJM 2017 DOI: 10.1056/NEJMp1704485


VS.

PQRST Index for rewarding research

"To change the tide, the criteria by which scientists and their teams are rewarded for their efforts by agencies that fund them and institutions that host them should be revisited, aligning criteria with the desired outcomes: research that is productive, high-quality, reproducible, shareable, and translatable [PQRST] …funding agencies, universities, research institutions, academies, professional societies, and prestigious award organizations may also have PQRST indices based on the research work they sponsor or perform and the scientists behind this work."

Research to Publication eLearning programme

Research to Publication (RtoP) is an eLearning programme for early career academics in healthcare research to guide them right through from designing a study to seeing it published in an international journal

RtoP offers a comprehensive and flexible set of stand-alone, self-study modules that let learners choose what to study, and at their own pace

RtoP draws on expertise of The BMJ's senior research editors and senior academics at the UCSF Clinical and Translational Science Institute

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http://rtop.bmj.com

http://rtop.bmj.com/

RESEARCH TO PUBLICATION

About Researchers Institutions Pricing Register or Sign In

BMJ

How to write & publish a study protocol

Understand different meanings of the term "protocol"; Communicate the value of planned research; Appreciate the characteri...

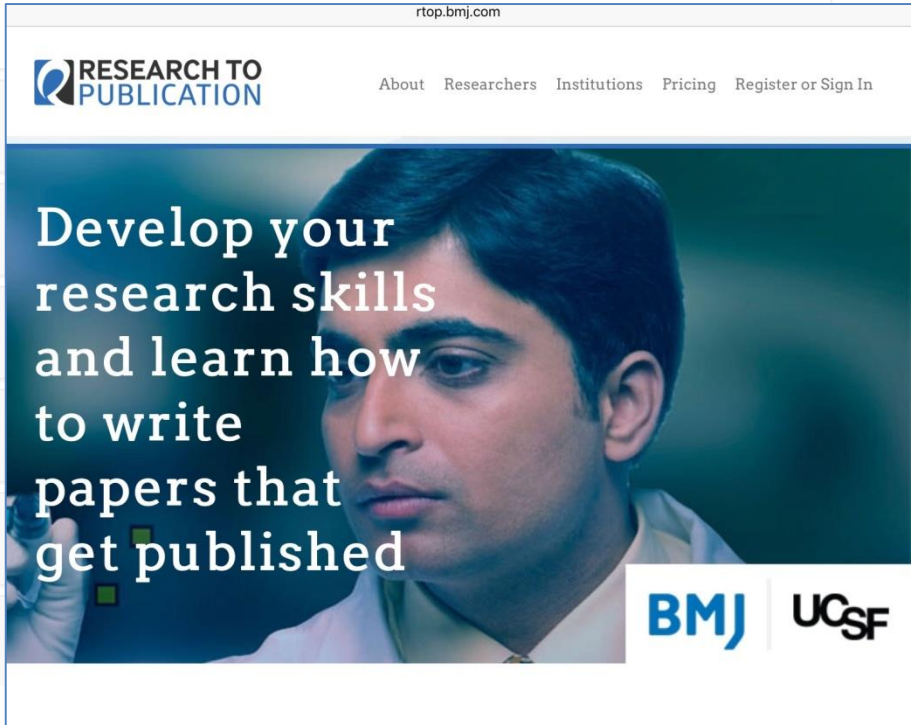
UCSF

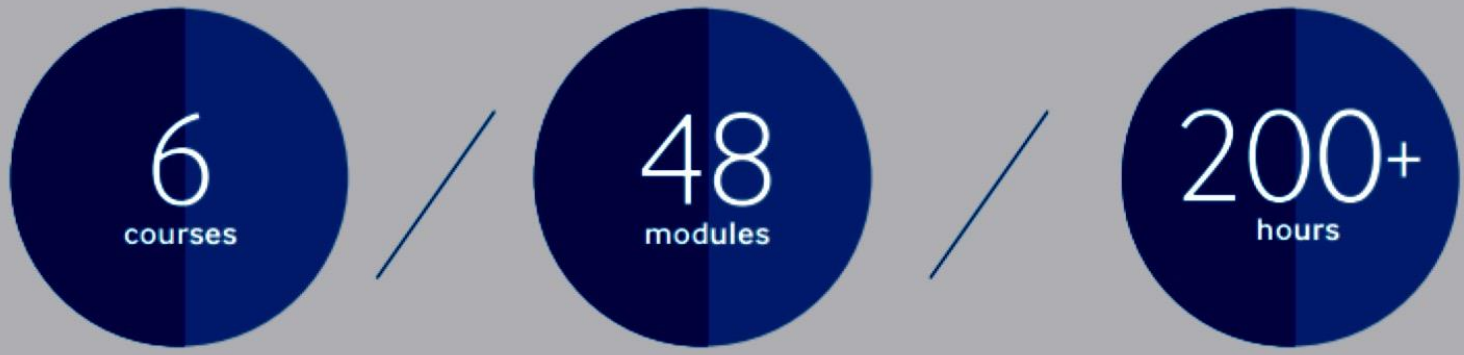
Introduction to randomized blinded trials

Define randomized blinded trials; Explain how to design RBTs; Describe how to choose the intervention and control conditio...

> *Discussing and undertaking the activities in this module was very exciting*
>
> Other, Public Health Medicine and Epidemiology, NG
> Module: Introduction to Randomized Blinded Trials
> 18.08.2016

- How to Write a Paper
- What Editors and Peer Reviewers look for
- Publication Ethics
- Designing Clinical Research
- Responsible Conduct of Research
- Introduction to Clinical Trials





Self-directed online study

Flexible learning

Video lectures

Narrated slides

Reading materials

Assessments (MCQs)

Certificate of completion

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The faculty

Professor Deborah Grady
Associate Dean of Clinical and Translational Research, UCSF School of Medicine

Professor Bernard Lo
Professor of Medicine Emeritus, UCSF CTSI

Dr Trish Groves
Head of research, BMJ; Editor-in-chief BMJ Open & Editorial lead for Research to Publication

RESEARCH TO PUBLICATION

BMJ

The introduction: presenting the research question

★ ★ ★ ★ ★ *(1) Rated by learners*

Resume section

Reviews

"It's a perfect section. Internal Medicine Resident. "
29.11.2016
Specialist Trainee/Resident, MX

"Excellent "
06.11.2016
Specialist/Consultant, Cardiothoracic Surgery, GB

"it was good and shows my common mistakes"
05.11.2016
Other, Psychiatry, ET

"Succinct advice!"
23.09.2016
GP/Family Physician, General Practice, BW

Learning Outcomes

Learning outcomes

At the end of this module the learner will be able to:

- Understand the purpose of the introduction section
- Explain what was known, and not known about the study's topic and about the specific research question
- Report the study's research question clearly
- Understand what makes a good research question
- Use evidence based, effective writing to introduce the study
- Use references/literature review effectively and sparingly.

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All audiences | More

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The importance of research protocols

Resume module

Written by:
Trish Groves

Reviews

BMJ Learning

The importance of research protocols - test yourself

1. Your department has had a strategy meeting where it decided it would start a prospectiv cohort study, in which patients with type II diabetes will be followed up over one year and have, every two months, digital photography of their retinas. This is specifically for the purposes of the study and these patients would not normally be examined so frequently. have been asked to write the research protocol.

   Which is the most important reason for creating a research protocol?

   a. Having a protocol will make it easier to get funding for the study

   b. Making the protocol available to staff who will recruit patients into the study will ma patient enrolment quicker

   c. The protocol could be published

   d. Writing a protocol is an ethical requirement

   e. You will benefit from the academic exercise of writing a protocol

The ethical requirement to have a protocol

Learn more about how international standards on research ethics require a protocol for any human study.

International standards on research ethics require a protocol for any human study

WMA Declaration of Helsinki 2013 requires that:

> the design and performance of each research study involving human subjects must be clearly described and justified in a research protocol
>
> the protocol should state the ethical considerations involved
>
> the protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study

0:29 / 1:16

Further study

Below we have presented a copy of clause 22 from the World Medical Association's Declaration of Helsinki. Read through this to understand why a protocol should describe and justify research involving human subjects.

You may also wish to read the full Declaration, last updated in 2013. [2]

Value for learners and their institutions

- uniquely, combines expertise of international medical publisher and world-leading university
- focused on clinical and public health research
- supports research integrity and drives high ethical standards
- builds research skills
- increases relevance and quality, of research; reduces waste
- improves chances of publication
- provides practical advice in a user-friendly multimedia format
- helps institutions build research capabilities, improve reputation, attract funding
- offers the option for integration into a Masters programme
- Certificate of Completion from BMJ and UCSF for every module
- 75% discount on APCs for protocols published in BMJ Open and other BMJJs

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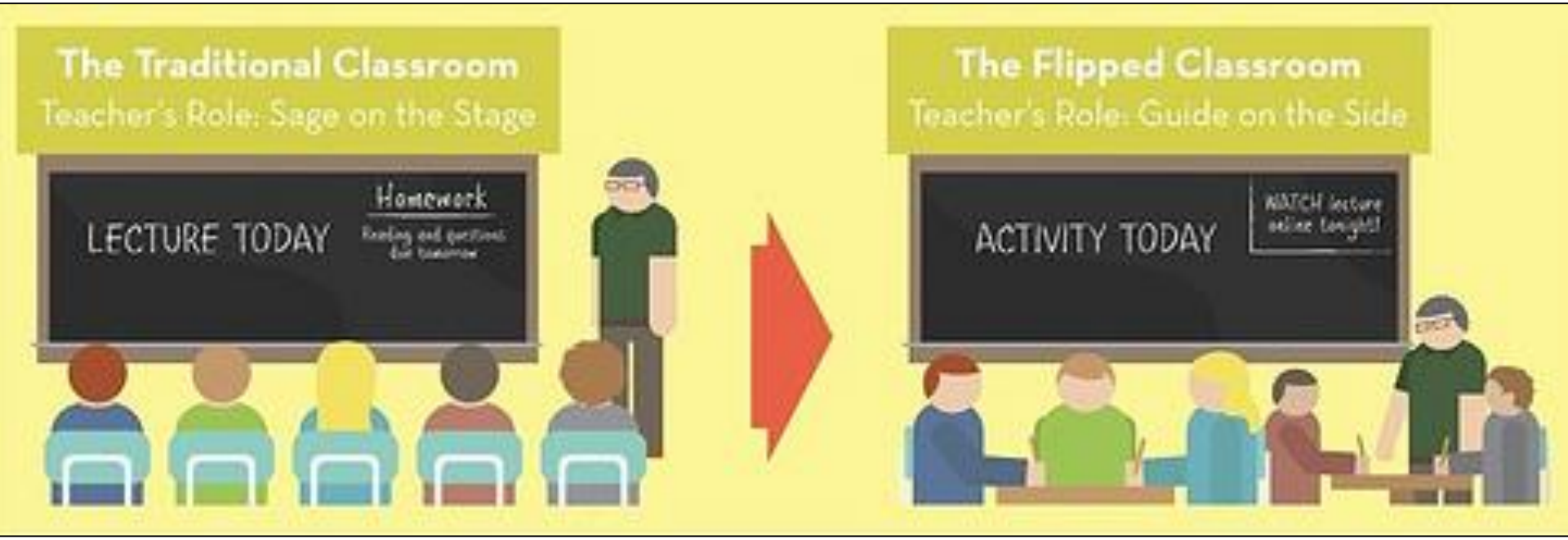
Ideal for blended learning with “flipped classroom”



- takes the lecture out of the classroom and brings homework in
- puts students in charge of their own learning
- students needing more time to master a concept aren’t left behind

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	Before the flip	After the flip
Before class	• students assigned reading • instructor/teacher/tutor prepares lecture	• students guided through learning module that asks and collects questions • instructor prepares learning opportunities
Beginning of class	• students have limited information about what to expect • instructor makes general assumption about what is helpful	• students have specific questions in mind to guide their learning • instructor can anticipate where students need the most help
During class	• students try to follow along • instructor tries to get through all the material	• students practise skills • instructor guides the process with feedback and mini-lectures
After class	• students attempt homework, usually with delayed feedback • instructor grades past work	• students continue applying their knowledge skills after clarification and feedback • instructor posts any additional explanations and resources as necessary, and grades higher quality work

Current learners with BMJ RtoP

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RESEARCH TO PUBLICATION

Thank You

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Appendix:
more details of modules

Course: how to write a paper

- the introduction: presenting the research question
- the methods: matching study designs to research questions
- ethics aspects of study methods
- reporting statistical methods and analyses
- the results: reporting all findings succinctly
- the discussion: using structure and balance
- choosing and citing references
- optimising the abstract and title

Course: what editors and peer reviewers look for

- compliance with journal and ICMJE requirements
- navigating journal and peer review processes
- surviving peer review
- what to do with rejections and appeals
- pre-submission inquiries and cover letters
- good medical writing

Course: publication ethics

- patients' consent to publication
- journal rules on authorship
- reporting conflicts of interest
- how to write up industry-sponsored trials
- scientific transparency: the pitfalls of selective reporting
- how and why to avoid plagiarism
- how journals uncover scientific fraud
- how journals act on scientific misconduct

Course: designing clinical research

- the research question
- study design
- subjects and variables
- enhancing causal inference
- sample size and power
- data and safety monitoring
- questionnaires and qualitative research
- ethical considerations in research

Course: responsible conduct of research

- overview of clinical research regulations
- informed consent and related issues
- conflicts of interest
- authorship and research misconduct
- ethics in big data and “precision medicine”
- research in resource-poor environments

Course: introduction to clinical trials

- trial designs
- randomisation
- selection of participants
- blinding
- choosing interventions and controls
- recruitment
- adherence and follow up
- outcome measures
- adverse events
- regulatory issues
- ethical issues in clinical trials