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Lock, Stock and Barrel:
Is it possible, practical or popular to publish everything?

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Objectives

- Review recent debate regarding the drive towards publication of all clinical trials
- How far can we/should we go?
  - What are the benefits?
  - What are the barriers?
- Potential solutions?

What does ‘publish everything’ actually mean?

Publish?

- Publish in peer-reviewed journal? Or sufficient to post results on publicly accessible database/web page?
- Does ‘publish’ always mean ‘publicly accessible’ (e.g. open access)?
- Does ‘publish’ always mean ‘independent’?

Everything?

- All clinical trials? Or preclinical/discovery as well?
- What about post-hoc analyses?
- Analysed data, raw data, or both?
- Only from now onwards? Or old studies as well? How far back?
- Only marketed drugs or failed drugs as well?
- What about failed studies, poorly designed trials, exploratory studies?

What do current regulations say?

- US – FDA Amendments Act of 2007
  - Post trial results on clinicaltrials.gov database
  - Only drugs with US marketing approval or cleared/approved biological or medical device
  - All phase II–IV studies in licensed indications
  - Submitted 12 months after trial completion (LPLV)
  - Tabular format, no peer review, no interpretation
- EudraCT
  - Post results on EudraCT
  - End 2012
  - All phase II–IV studies with at least one site in Europe
  - Regardless of marketing approval status
  - 12 months after trial completion (6 months for paediatric studies)
- Regulations do not specify need to publish in peer-reviewed journals

. . . and the publication guidelines?

- IFPMA/EFPIA/PhRMA/JPMA Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009
  - Disclosure of summary results in any free, publicly accessible internet-based clinical trial database (commercially available drugs)
- IFPMA/EFPIA/PhRMA/JPMA Joint Position on the Publication of Clinical Trial Results 2010
  - All industry sponsored trials should be considered for publication in the scientific literature
  - At a minimum, results from all Phase III trials
  - And trials of significant medical importance
  - Includes products whose development programs are discontinued
  - Submitted, where possible, to peer-reviewed indexed journals
  - Within 12 (and no later than 18) months of trial completion, marketing approval, or decision to discontinue development
- GPP2 – endeavour to publish results of all clinical trials of marketed products

Full access to trial data?

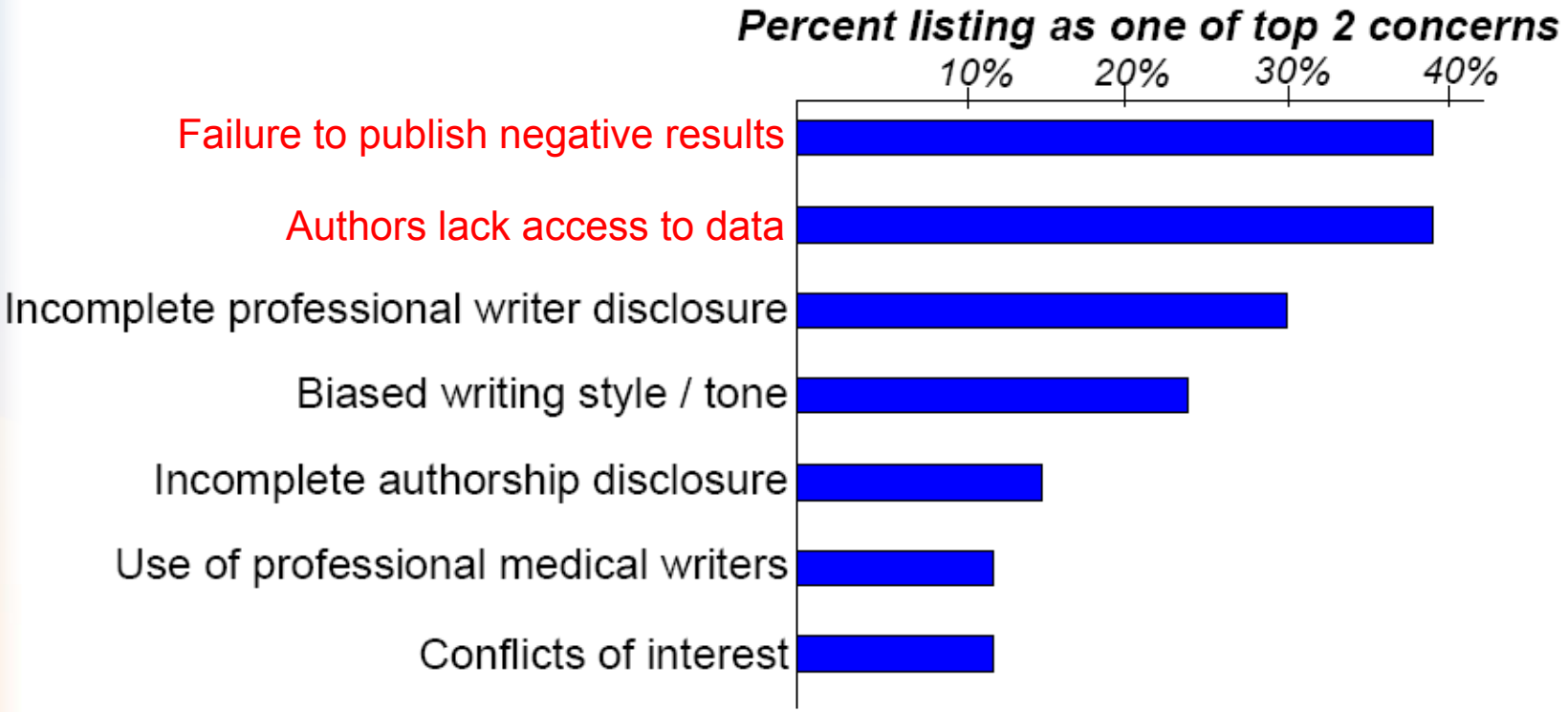
- Focus of several BMJ articles during 2011
- An article on opening up data at the European Medicines Agency
- One suggestion – governments and policy makers should ensure public access to data before they licence or purchase drugs
- New initiative by the Wellcome Trust sets out some guiding principles
  - 17 research funders collaborating to increase availability of data from research that they fund (though no method of enforcement)
  - "*In the meantime, a modest recommendation to the medical research community: get used to it*." Vickers AJ. BMJ 2011;342:d2323

Publish all data?

- BMJ – have mentioned a theme issue on ‘unpublished evidence’ planned for December 2011
- “. . . *the existing evidence base, composed as it is of clinical trials, systematic reviews, and meta-analyses . . . may be missing key information*.”
- “*We are especially interested in high quality original research that aims to uncover previously unavailable data and to re-evaluate treatments and practice in light of that new evidence*.”

MPIP survey of journal editors

What are the 2 most outstanding unmet needs to address in order to improve the credibility of industry-sponsored research?



*Online survey completed by 33 editors (of 302 invitations); mix of editors-in-chief, deputy editors and other senior editors: ~12% ex-US and ~85% from journals specialised by therapeutic area

The case for publishing everything

- Publication bias
  - Imbalance of positive vs negative studies → distorted perception of treatment effects
  - Unpublished evidence skews meta-analyses, systematic reviews, clinical practice guidelines
  - May negatively affect choice of comparator in comparative effectiveness studies
- Reduce patient risk and advance medical research
  - Negative data and failed products can enlighten future research
  - Avoids subjecting more patients to the same negative trial outcome
- Clinical practice decisions need to be made on full evidence base (patient safety)
- Failure to disclose negatives studies drives up medication costs
- Full data availability
  - Allows independent or different analyses and interpretation
  - Removes potential bias
- Not possible to decide what studies might/might not affect future clinical practice
- Commitment to transparency will increase trust in the pharma industry
- We owe it to those who participated in the trial

Survey of publication professionals

- Survey conducted 2–21 August 2011 (SurveyMonkey)
  - ISMPP members
  - AMWA members
  - NetworkPharma community
  - Other relevant groups on LinkedIn
- Up to 20 questions (dependent on participant response)
- Eligible – professionals involved in developing, planning, publishing medical publications
- Completed surveys evaluated using descriptive, univariate analysis
- 739 respondents of which 679 were eligible
- 607 completed the survey and were analysed

Woodrow R et al. Presented at 2011 European Meeting of ISMPP, November 2011

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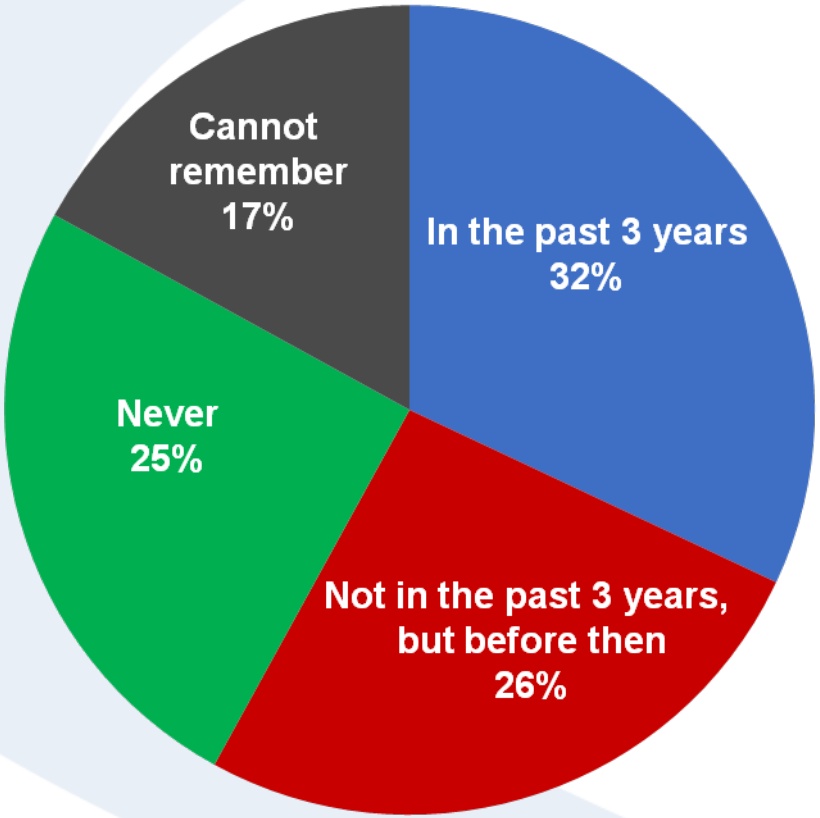
Awareness of negative data from ANY clinical trial not being published by a pharmaceutical company



Reasons for not publishing

- Compound discontinued (40%)
- Journal rejection (36%)
- Poor trial design (31%)
- Lack of resources (budget, staff) (27%)
- Damaging to product profile (27%)
- Lack of thought/discussion about making data public (22%)
- Investigators unwilling to publish (20%)
- Data superseded (14%)

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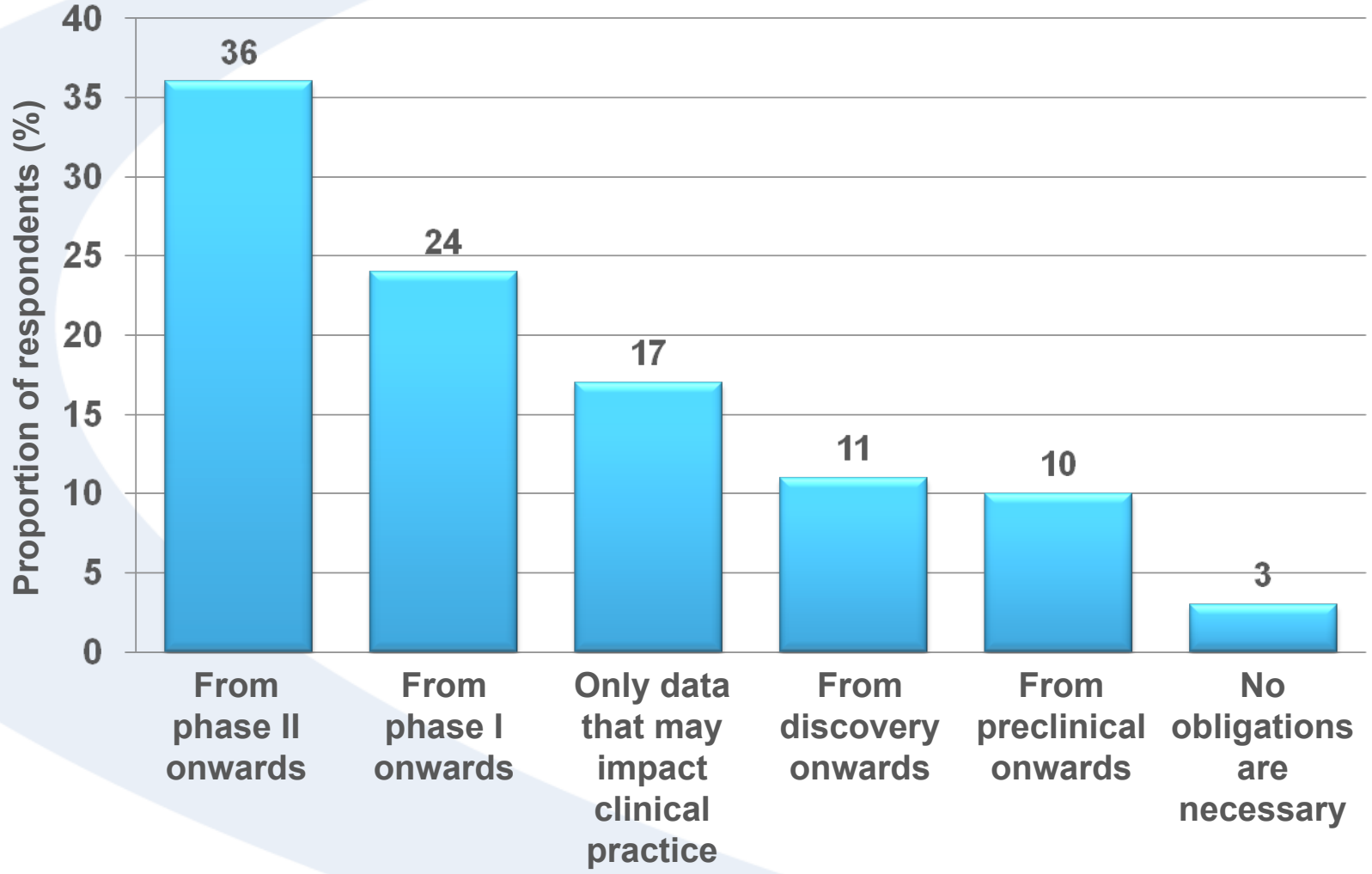
From THE CURRENT TIME onwards, should companies be obliged to make trial data available?



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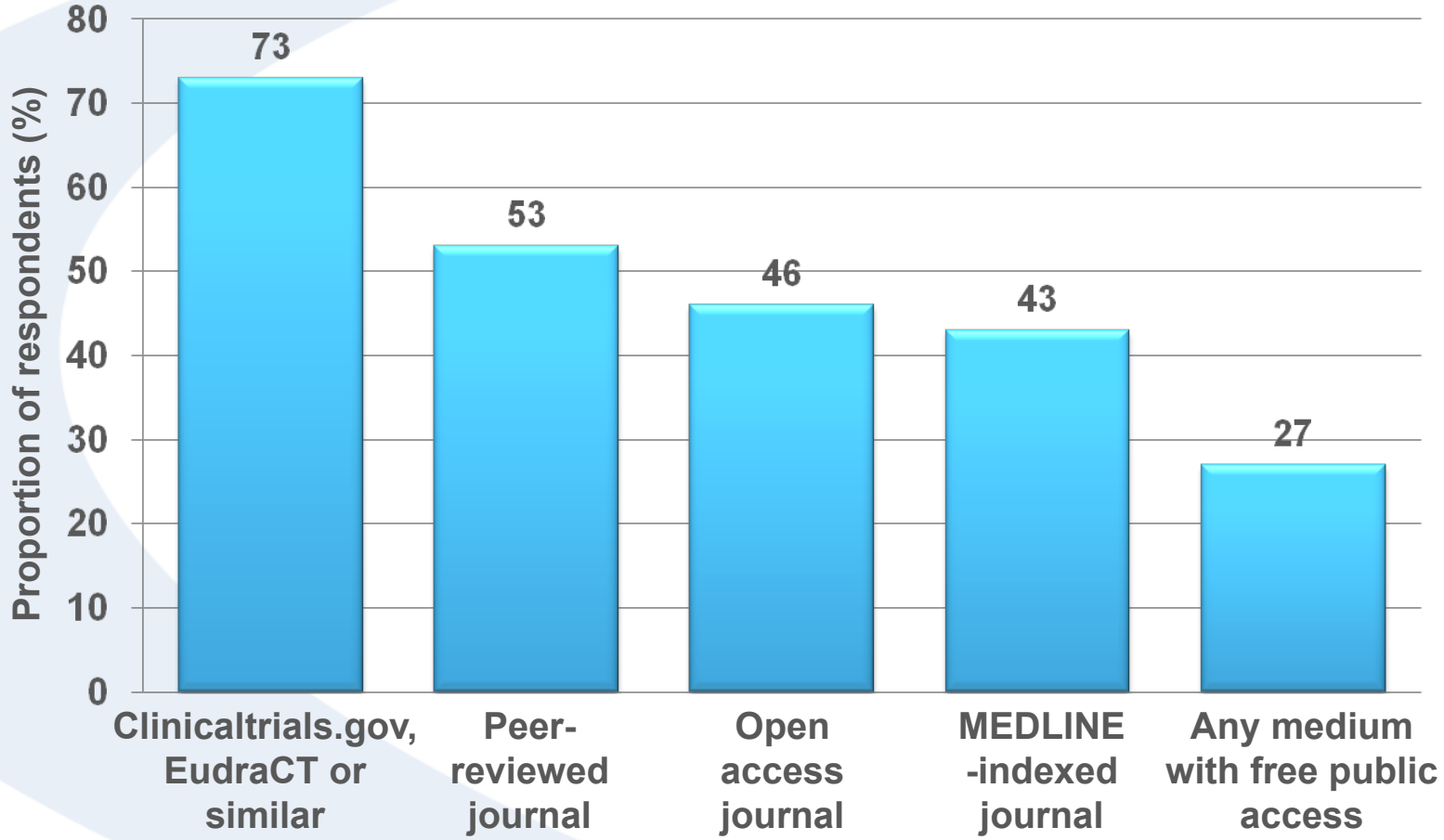
What media would suffice as making the data public? (Top selections shown)



More than one category could be chosen

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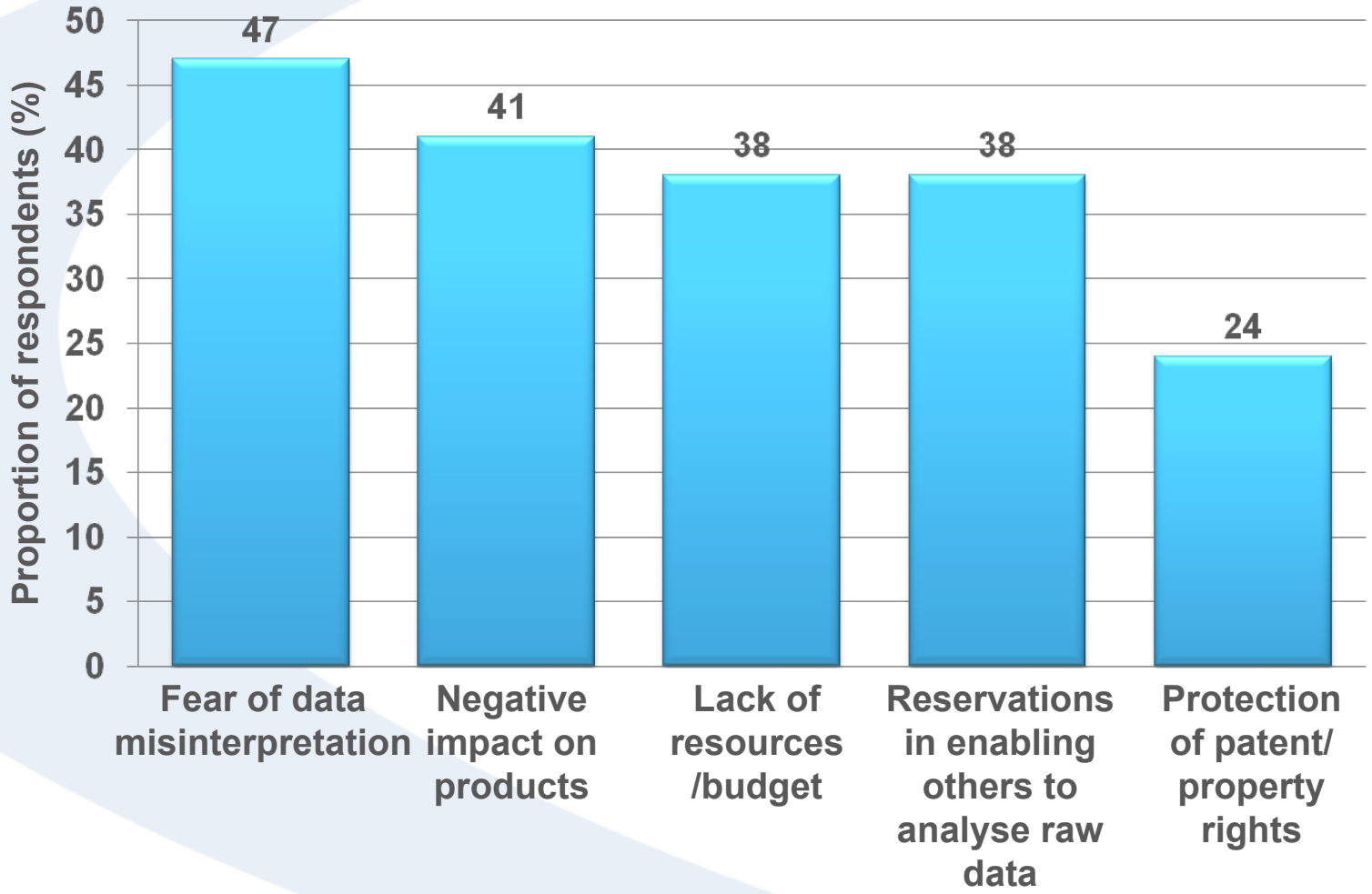
What are the MAIN barriers to publishing all data from now onwards? (Top selections shown)



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More than one category could be chosen

Barriers to publishing everything

- The appeal of the impact factor (IF)
  - Journals fear IF will be affected (negative research rarely cited)
  - Authors do not want to publish in low tier journals (academic progression/CV)
- Open access
  - Cost of publishing (article processing fee)
  - Unfamiliar with open access
- Clinical trials.gov/EudraCT
  - No interpretation, study limitations
  - Fear of misinterpretation/misrepresentation (HCPs, public, media, lawyers)
- Waste of resources
  - Detracts from focus and spend on R&D
  - Makes drugs more expensive
- Failed drugs
  - Internal resources and budget diverted elsewhere
  - Systems and processes no longer in place
- Company commercial interests
  - Protect data of commercial interest (e.g. to study another indication)
- Scepticism – will it really lead to increased trust in the pharma industry?

How much information should be made available?

Raw data

- May not be useful to the average audience (and may be dangerous)
  - Sorting the wheat from the chaff; may be 1000's of pages
  - Poor interpretation or extrapolation could harm patient well-being
  - Open to abuse or misuse: re-analysis by those with a vested interest (e.g. competitor companies, lawyers)
  - Does raw data alone really help transparency efforts?
- Regarded as pre-publication by journals?

Exploratory studies

- Need to be interpreted with caution – only analysed and interpreted data?

Failed studies/drugs

- May help direct future research, but depends on reason for failure

Should we retrospectively release unpublished data?

- Ideally yes, but practical considerations
  - What type of studies/data? How far back?
- Traditional journals unlikely to publish unless interesting data
- Study investigators/company statisticians
  - Are they still around? Willing to author a retrospective paper?
- Study sponsor
  - Do they have resource/budget? If a failed trial/drug, why invest more cost?
  - Is data easily retrievable (companies may have merged, data storage systems changed)
  - Fear of 'bad press' and litigation?
- Therapy area
  - Scientific field may have progressed – base interpretation on what was known at the time or what is known now?
  - Analytical practices changed? Clinical guidelines changed?
  - Is study rationale still relevant?
  - Has evidence from 'real-world' usage superseded what was observed in the trial?
- Add stipulations
  - Only marketed products and products in development?
  - Not off-patent or discontinued products?
  - Only studies that impact clinical practice or phase I onwards?
  - But who makes this decision?

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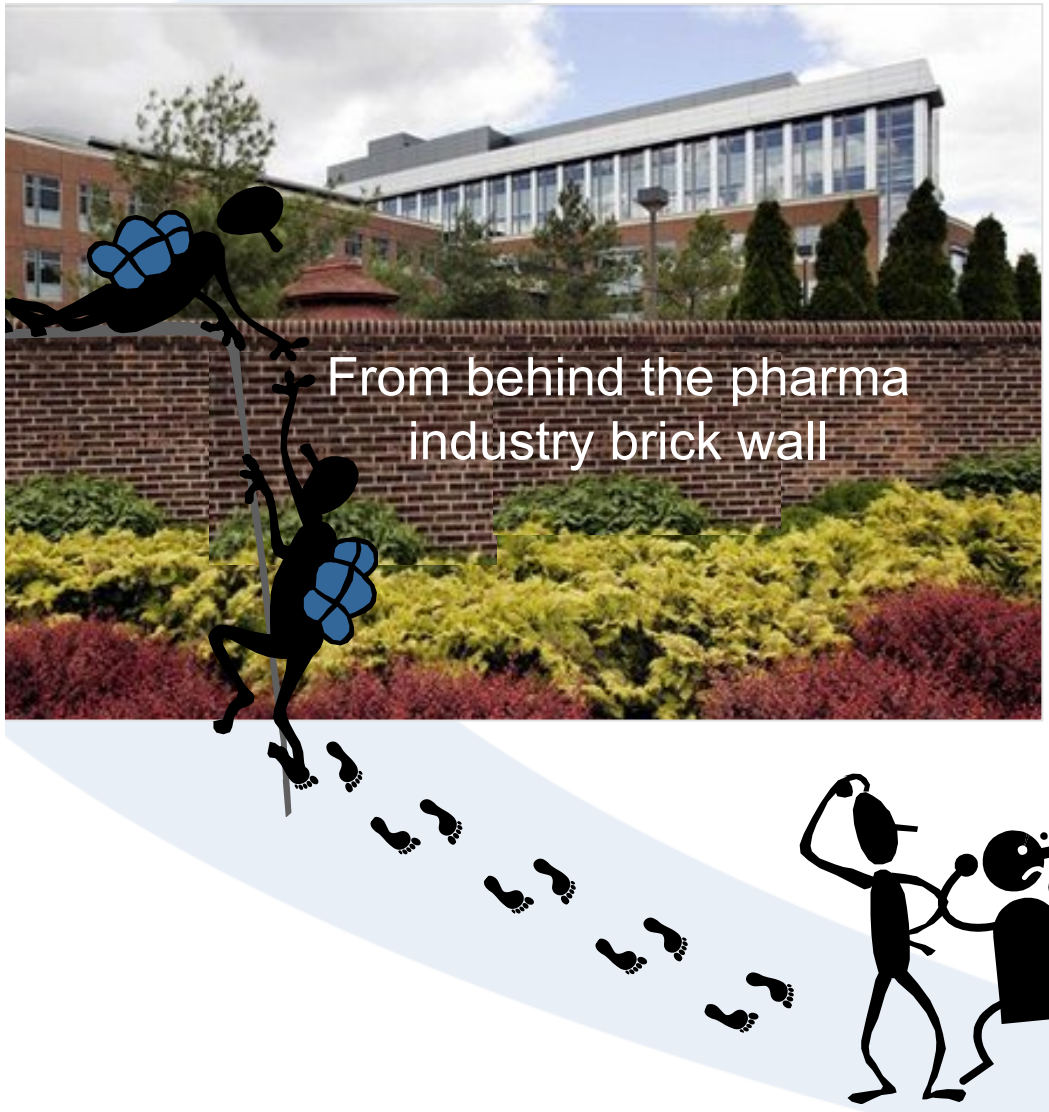
If not open access or web-based, are we any further forward?



Potential solutions

- Aim to publish all new studies at least from phase I onwards in peer-review journals
- Publish negative/inconclusive/small studies (provide interpretation)
- Use wider publishing options (ignore impact factors)
  - Open access journals (ideal)
  - Journals that offer supplementary digital content
  - Specific journals that accept negative data
  - At minimum, post results on publicly accessible database
- Publish CTRs on company website (or government website if expanded) (product promotion?)
- Make raw data easily available upon request
- Engage external expert panel to adjudicate if concerns that data may be detrimental to patient wellbeing (e.g. poorly conducted studies)
- Make decision on data dissemination route a key part of publication plans (avoid internet burying)
- Develop decision criteria and guidelines for making ‘old’ study data accessible
- Should apply to academic and government research, not just pharma
- Need set of reasonable criteria to follow in different circumstances
- Be prepared for future regulatory/government mandates

Summary

- Journal editors see failure to publish negative results as one of the unmet needs in improving the credibility of industry-sponsored research
- Many medical publications professionals are aware of unpublished negative data
- Strong argument for wider and easier access to data
  - Summarised data on clinicaltrials.gov or EudraCT may be insufficient
- Large voice of opinion that clinical trial data before phase II should be made available
  - Earlier that what US and EU regulations stipulate
- Several potential barriers to be overcome to publishing all data
  - Many are surmountable
- Question as to how far back we should go to make unpublished data available
  - Clear rationale required for what is reasonable

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Thank You!

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