foreign corporations to sue governments for compensation where vested interests are threatened. In turn, it may have a 'chilling effect', dissuading governments from introducing effective health, social and environmental protection policies if it is considered likely that they will be contested by industry. Pertinent examples already exist, e.g. a pharmaceutical company seeking compensation for national court patent ruling; and of the tobacco industry suing a national government over the introduction of standardized ‘plain’ tobacco packaging. The EC ‘reform agenda’ does not ‘satisfy the criteria of independence, fairness, openness, subsidiarity, or balance’ and the recent failure of the European Parliament to reach agreement on it signals a strong EU opposition. By its own analysis, the Commission should remove the ISDS from the TTIP completely and leave justice in the hands of national courts.

So, what Europe do we want? United Europe is a construct developed for economic growth and prosperity but one that must also invest in and protect the equity, safety and happiness of its citizens. It should be mobile, innovative and outreaching but in doing so champion and defend its values and integrity rather than trade them for profit. There are ways to improve existing and future trade agreements and rules making them more globally equitable and socially responsible: placing equity and development (not trade) at the centre of the treaties; implementing explicit exemption of critical goods and services, e.g. health; and introducing obligatory labour, certification and environmental standards. The details of such ‘social clauses’ may be up for debate but the process should be transparent and must include the participation of relevant professionals and civil society.

Supplementary data

Supplementary data are available at EURPUB online.

Credibility of observational studies: why public health researchers should care?

Much medical research including clinical or public health comes from observational studies, that represent 9 of 10 research papers published. The rigour and trustworthiness of research is, in large part, based on a priori planning and documentation of a methodical approach to conduct that is usually reported in a protocol. Scientists are used since decades to elaborate study protocols for the approval from independent ethics committee, well before the study begins. Pre-registration of epidemiologic study protocols on publicly available websites and on scientific journals, however, is a debating issue since few years. Among those in favour, some issues have been raised to support the importance of a clearly reported protocol: (i) it allows scientists to carefully plan an observational epidemiologic study and thereby anticipate potential problems; (ii) it allows reviewers to explicitly document what is planned before enabling the study begins, to compare the protocol and the completed study, to replicate the methods if desired, and to judge the validity of planned methods; (iii) it enables readers to identify deviations from planned methods in published reports and whether they bias the interpretation of results and conclusions; (iv) it might help funders, in order to check the status of the study in terms of inception, ongoing work and published reports. Finally, a publicly available protocol has in principle the potential to prevent from selective reporting biases, that is selecting the results on the basis of a subset of the original variables recorded to be included in a publication.

Overall, publicly available study protocols have the potential to increase the credibility of the scientific literature. Since 2007, modifications on ClinicalTrials.gov were made to accommodate elements used for registering protocols for observational epidemiologic studies. Recently, we reported that until 2014 the registration of observational studies on ClinicalTrials.gov was far from being optimal, as it used to occur after studies have started, and pre-specification of secondary outcomes and statistical analysis almost never occurred. A potential remedy for this situation relies on the development of a set of standard items (e.g. a checklist) that should be included in an observational study protocol, and the development of a dedicated website for registering such protocols. A series of papers recently published on Lancet reported that 85% of research resources are wasted, and recommend that few effective interventions are needed to improve the credibility and efficiency of scientific investigation. Among them, a recurrent recommendation claimed that funders should insist on publication of protocols at study inception, and encourage collaboration to reduce waste; monitoring—periodic surveys of progress in publishing protocols... "Make publicly available the full protocols, Monitoring—proportion of reported studies with publicly available (ideally pre-registered) protocol... within 6 months after publication of a study report"; "Investigators, funders, should systematically develop and adopt standards for the content of study protocols..."
Concerning systematic reviews and meta-analyses, and intervention studies, in the past 2 years guidance for drafting research protocols have been published (PRISMA-P and SPIRIT checklist, respectively), along with dedicated websites (http://www.crd.york.ac.uk/PROSPERO/ and http://www.clinicaltrials.gov, respectively). Though the endorsement by scientists of such guidance checklists is impressive, no one guidance for observational epidemiologic study protocols has been developed so far.

Though I acknowledge all the cons that have been raised and partly discussed in the reply of Jan P Vandenbroucke, I strongly believe that in the long run the advantages for the scientific community of pre-registration of study protocols will outweigh any potential disadvantage. In the meanwhile, coordinated efforts towards a funding system systems that truly award scientific research based on grounded epidemiological methods, on transparency, and on shared materials, and education efforts focused on journal editors, would contribute in the direction of improving the quality of scientific research.

References


The debate about preregistration of protocols of epidemiologic studies had become an intellectually divisive issue, with strong ‘pro’ and ‘contra’ positions. The pro side, of which the commentary by Stefania Boccia in this issue of the journal is an example, is unflinching: all observational research needs to be preregistered to make it credible and manageable, in particular to root out the possibility of selection bias. The great exemplar is the randomized controlled trial (RCT). This pro side has never paid attention to the reasons why the contra side thinks that the need for registration and the need for sticking to the preregistered protocol may depend on the issue that is researched. The contra side does not tire to point out that when one tries to explain how Nature works, one is chasing a problem; when chasing a problem one tries all kinds of approaches, and it does not matter what the original thoughts were and how and why ideas have evolved. The only thing that matters is the final proposition to the scientific community: an explanation together with the corresponding data. The scientific community will then decide whether the ideas that are presented are useful as a start or a continuation of further expansion of knowledge. That is entirely different from the reasons for which preregistration was necessary for RCTs: the well-being of millions of patients across the globe may hinge on one or two RCTs (funded by very interested parties) and one does not want the whims of an investigator to define some subgroup or some alternative analysis after seeing the data. In contrast, exactly that kind of flexibility is necessary when chasing the solution of a problem of disease causation.

The contra camp has proposed that there are exceptions: ‘Consider a heated controversy concerning a topic with large societal and economic consequences, in which conflicting results have been obtained, perhaps even by analyses from the same data. To make progress, this might be an instance in which stakeholders sit together beforehand to agree on a protocol that will convince everybody. The main purpose of such actions is not “prespecification”; however, it is to bind stakeholders (who may distrust the other’s analyses) to a procedure they all trust’. To date, we have not heard of a proposition for differential application of preregistration from the pro camp.

The fundamental deficit of the pro position is that it only reasons in terms of methods and procedures of numerical research. The idea that checking a list of methods and procedures will lift us out of a problem is tantamount to Baron von Munchhausen’s attempt to lift himself out of a swamp by pulling at his own hair. Much like rising from a swamp demands levers from the outside, the solution of a problem of disease causation demands the integration of diverse types of scientific knowledge: numerical, clinical, pathophysiological and basic science. For this integration, there are no rules—it is done on a case by case basis. Sometimes methodology of numerical research plays an important role, at other times not. That is again very different from the RCT situation where a final decision has to be made based on a couple of numerical studies.

Preregistration: when shall we start the real discussion?

Eventually, the idea of universal registration of observational research is bound to practical failure. In an RCT, the moment of randomization is a clear dividing line: the data that are obtained after randomization are not looked at, except for interim safety analyses, and only analysed at the very end. In observational research, this dividing line is mostly non-existent. Databases have already been looked at to see whether the research question can be solved by the data; often the data are very complex and one has to learn their strengths and weaknesses when doing the analysis— or the failure of some analysis brings about ideas about a better way of progressing. The same almost always happens in systematic reviews, also of RCTs: those who draft a protocol for a systematic review already know several important RCTs (which are the data of the systematic review), and they know the reasons why the results of these studies led them to do a systematic review. To maintain that

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