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Medical registries represent vital patient interests and should not be dismantled by stricter regulation

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ABSTRACT

Background: Medical registries serve patients as beneficiaries of quality standards and new treatment opportunities. However, it has been argued that registries threaten patient privacy interests and should therefore be more strictly regulated.
Methods and Results: With the European Treatment and Outcome Study for Chronic Myeloid Leukemia as a concrete example we identify and describe how four of the major arguments put forward for stricter regulation fail.
Conclusion: We conclude that medical registries should be promoted both for research and quality control, and that the regulatory bureaucratic burden should be reduced.

1. Introduction

Although the randomized trial is the gold standard for evaluating the efficacy of a treatment and provides results of high internal validity there are inherent limitations with regard to the generalizability of the results to routine health care. Randomized trials recruit preferentially highly selected patients [1] and the suitability of study centres and the qualification of the physicians have been checked by IRBs and ethics committees. Therefore, the external validity of the results of RCTs has repeatedly been questioned [2]. Thus it is important to find out whether the new superior treatment has been adopted and whether the outcomes in routine health care are comparable to those found in the RCTs. Assessment of treatment outcomes in real world clinical practice requires good clinical registries with relevant and validated data based on standardized diagnostic methods that make it possible to monitor individual patient outcomes at different stages of the disease. There is increasing evidence that individual hospital data will not give the detailed insight needed and therefore large national and transnational registries are necessary [3]. For rare diseases in particular, the network of clinical registries for this collaborative gathering of data has to be wide-spread, comprising many clinical centres on a global level.

Medical registries serve accordingly vital patient interests but they have been criticized for jeopardizing privacy concerns and proposals have been made for stricter regulation. We will investigate one recent proposal in some detail but will first provide a concrete example of a well-functioning registry network in order to give a realistic background to the ethical discussion. As a result of the Swedish EU Presidency Conference "Assessing Drug Effectiveness" in July 2009 an initiative was taken to collect information about some promising clinical networks in order to define factors of success and hurdles encountered from a drug effectiveness perspective. One of the registries identified was the EUTOS network (European Treatment and Outcome Study for Chronic Myeloid Leukemia).

2. EUTOS – a case study

Chronic Myeloid Leukaemia (CML) is a malignant neoplastic disease of the human myeloproliferative system and is linked with the 'Philadelphia chromosome', a reciprocal translocation of chromosomes 9 and 22. In most European countries very little is known about the regional epidemiology of the disease. CML constitutes about 15% of all leukaemias, and has an estimated

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age-adjusted incidence of 0.6–2 per 100,000 persons per year [4]. There are currently three main treatment options: symptomatic palliative treatment, stem cell transplantation, which is potentially curative, but depends on the availability of a donor, and is still associated with considerable early mortality; and as first line treatment tyrosine kinase inhibitors (TKIs), orally administered drugs that in a great majority of patients achieve considerable reduction of tumour burden and therefore also prolonged survival. The EUTOS for CML Registry started 2007 as part of the EUTOS for CML project. This, in turn, is a collaborative project between *Novartis Oncology* and the European LeukemiaNet (ELN). ELN, a network of excellence funded by the European Commission, comprises hundreds of leukaemia centres and study groups and thousands of investigators and scientists in 32 countries caring for more than 10,000 patients.

The EUTOS for CML Registry collects baseline, treatment and outcome data for patients with CML across Europe. It is divided in to three subregistries:

- *In-study*: patients diagnosed between 2002 and 2006 from national study groups enrolled in prospective trials, who were taking *imatinib* (the first introduced TKI) as first line treatment (currently 2389 patients)
- *Out-study*: patients diagnosed between 2002 and 2006 already registered in existing databases, who received *imatinib* frontline (currently 1536 patients).
- *Population-based*: all newly diagnosed patients in prespecified regions of 24 European countries from 2009 onwards, irrespective of frontline treatment (currently 1185 patients).

This collaborative data gathering and subsequent analysis is aimed at gaining information about: (1) Factors that allow prediction of the future course of disease. Validated prognostic models that support individualized treatment. (2) The epidemiology of CML across Europe, with particular emphasis on the frequency and the prevalence of a disease that due to the success of current therapy is increasing by 10% per year and can give rise to economic and social issues [5]. In addition data on the initial clinical management are collected to find out whether there is any type of limited access to the treatment of choice, be it based on sex or age. (3) The outcome of treatment. (4) The registry may also be used for assessment of the long-term safety of administration of this new kind of anticancer agents (TKIs), to a large number of patients.

A key idea of the EUTOS registry is to have a single central logistic infrastructure that gathers data, controls data quality, and assists the working parties in achieving their objectives. All participating CML study groups receive descriptive analyses of the data they have contributed at regular intervals. Incidence data will be estimated for all the participating 24 countries separately, stratified for age and sex. Particular care is taken to analyse the current management of CML patients using the ELN recommendations as reference [6]. The registry uses coded data and the identity of each patient is only known by their attending physician, unless otherwise specified by national regulations. Data are collected and transferred in strict compliance with national laws and regulations. Ethics Committee's review, information and consent procedures follow national regulations too.

The EUTOS for CML Registry is purely observational but of vital interest for patients with CML. Through this collaboration comprehensive prognostic models are being developed and validated in order to allow optimization of individual treatment choices [7]. Furthermore, the impact of therapeutic drug monitoring, pharmacokinetics and patient compliance is assessed, the sequelae of discontinuation of treatment after significant tumour reduction are evaluated and unexpected and late adverse reactions to drugs may be identified and assessed. All these objectives are of great clinical importance and would not be attainable without the collaborative data gathering and registry based approach.

3. Registries criticized for threatening privacy

Accordingly, vital patient interests are in the balance in association with the EUTOS for CML and other similar registrations and data-sharing efforts. However, within the ethics and legal literature collaborations between medical registries of this kind are seen as controversial because they pose a potential threat to the individual privacy of the patients. Mark Rothstein has recently argued that collection and use of large quantities of health information create a substantial challenge for protecting the privacy of patients and research subjects that is accentuated when biological samples are involved [8]. De-identification, he suggests, does not solve the problem since the process of removing identifiers implies that someone will actually have to do it thus representing an intrusion in private matters. It has also been claimed that re-identification may be possible by using publicly available databases, provided that one have access to reference samples [9]. Rothstein suggests that rules about de-identification are insufficient for privacy protection and need to be complemented with rules about notice provisions to patients, such as informed consent, strategies for opt-out, and giving individual patients a degree of control over the use of data and, where relevant, biological samples.

4. The critique fails for four reasons

In light of the experience with the EUTOS for CML registry we believe that Rothstein's argument fails for four reasons.

1. Rothstein foresees criticism of his proposal for leading to selection bias in research, delaying the introduction of new treatment and safety procedures in medicine, but he claims that at present there is an "insufficient empirical basis to assert that adding some level of privacy and autonomy protection to deidentified health information and biological samples will invariably and unreasonably disrupt biomedical research" (p. 8). However, as has been argued by several, inclusivity and universality are the keys to successful registry research [10,11]. There is a price to be paid since all requirements for informed consent, opt-out, re-consent, etc. imply that the registry will be affected both by those included and those not included. The likely result is incomplete information and data bank bias that will prevent researchers from tracking success and failure of treatment and drug efficacy and safety. The immediate victims of this will be the patients, with those suffering from rare diseases like CML paying the highest price. There are several examples of bureaucratic ethical review procedures and requests for consent that seriously jeopardized the possibility of doing biomedical research, at the end exposing patients to increased risks [12,13]. There are recent assessments available of the cost in lives caused by hurdles related to information and consent procedures [14].
2. Rothstein acknowledges that research concerns should not be dismissed lightly, but, he continues: "On the other hand, the interests of patients and the public also deserve respect and consideration" (p. 8). His argument for privacy relies, as stated, on a perceived dichotomy between the clinical researcher on the one side with the patient and the public at the opposite side, a normative description of the relationship that is questionable.

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This dichotomization seems to be a rather common phenomenon [15]. As Dixon-Woods et al. have recently argued, the ethical, legal and sociological accounts of medical research that influence the policy debates describe research as operating in opposition to the norms and interests of the general public and of the patient [16]. Based on empirical studies in a pediatric oncology research context they were, in contrast to this alleged dichotomy, able to show how sentiments of coalition and partnership characterized the relationships between the patient families, their doctors and the researchers.

3. Rothstein argues for the need of increased protection of privacy and autonomy based on these interests as fundamentally protected by constitutional law. Wendy Mariner argues in a similar vein for the need of limiting intrusion into medical privacy and has suggested that a constitutional challenge could dismantle cancer registration [17]. Health is regarded as an important concern but must sometimes give way to inherent principles of law, e.g. protection of privacy [18]. That privacy is a vital interest of citizens and democratic societies is not controversial. However, the values that are associated with a secluded life are all kinds of social value [19]. They presuppose and acquire their meaning only in a context where various kinds of social relationships with other individuals are involved. To be banished to seclusion on a desert island, certainly implies that one will be left in peace, but it is not the kind of situation which people wishing to protect their private life, strive for. Individuals, as far as their own personal matters are concerned, have an interest in being left in peace but they also wish to participate in the possibilities that are available to citizens in a society. This includes having access to new medical knowledge attainable only when personal medical data is recorded and shared within the format of large well-managed registries.

   In order to further strengthen his argument Rothstein suggests that autonomy is only one aspect of the broader concept of "respect for persons" (p. 8) and that this should imply closer regulation of registry research. However, patients have interests also at the end of the research line, e.g. in new possibilities to follow up the effects of medical drugs with regard to treatment response and adverse reactions, and if they became aware of the costs of stricter regulation undermining the possibilities of participating in the development of scientific knowledge they may be more likely to feel disrespected.

4. Rothstein is critical of partnership with commercial interests in association with biomedical research, something not uncommonly questioned by ethicists and lawyers [20]. However, we suggest that partnership between academic and commercial partners is essential for making progress in medical research and is intrinsic to concerns about assessment of drug efficacy, safety and effectiveness. This claim does not imply that one should be naïve. For the benefit of patients sharing of data should go in both directions, also when a pharmaceutical company enjoys a monopoly.

Potential conflicts of interest may arise and should not be taken lightly. The increasing collaboration between industry and patients' organizations should be considered. However ELN provides an interesting example of how doctors and researchers may be able to collaborate with the pharmaceutical industry while preserving their own integrity. A working party has just started a controlled trial in order to find out when treatment of CML patients with TKI should be stopped because the patient will not benefit from prolonged treatment with the drug. Such a study may, arguably, not be in the best (economic) interest of the drug companies.

5. Medical registries should be promoted for research and quality control

Development of medical registries with sharing of data is intrinsic for the protection of patient benefits and patient safety. If, linked to the medical record, and used also for clinical decision making in dialogue with the patient the benefit and legitimacy of clinical registries might increase even more. The patient in our view should have the right to quality assured medical treatment and care and the clinicians and hospitals should have a corresponding duty to document relevant quality measures for long term follow up of treatment. There is a well-recognized duty to document at the individual patient level but today there is a lack of systematic collection and analysis of aggregated registry data. It was objected by one reviewer that registries for quality assurance are seldom considered a problem from a data inspection point of view, because the exact use of data is clearly specified at outset and the registries are used for the same, usually repetitive quality assurance analyses while research implies that new questions are being raised as science develops. However, there is an increasing awareness of the need for aggregated data for quality assessments and drug efficacy/safety assessments. Recent developments in genomics in fact blur the traditional line between quality assurance and research through the rapidly increasing possibilities to identify genotypes as well as environmental factors regulating the treatment benefit/risk scenarios.

It is actually strange that the demand of mandatory quality assurance that is common in so many other areas in society is not implemented as rigorously in health care where lives are at stake each day. Furthermore, in order to assure the patient the best medical treatment available at each time research based on those registries is necessary and should in principle be approved and supported. From the patient's perspective there is no conflict between the interest of documentation in a medical record, the interest of follow-up and long-term assessment through medical registries (whether local, national or collaborative on a global level) and the interest of receiving the at each moment best available treatment based on research. This, we believe, holds not only for rare diseases like CML but also for all medical treatment.

6. Conclusion

The EUTOS for CML Registry clearly illustrates the benefits of aggregated, long-term clinical data for the assessment of drug effectiveness, in particular for orphan diseases but the same logic applies to all diseases, i.e. the more standardized, relevant and validated data available in quality registries, the better. Although values such as autonomy and privacy are important and should be safeguarded, it must be kept in mind that these registries exist for the good of patients and therefore it seems inconsistent and even unethical to hinder their optimal utilization. Transparency and safeguarding personal integrity are necessary to preserve trust but rules and legislations to protect integrity should not prevent the development of registries and performance of clinical trials in both national and transnational collaborations. That would be detrimental to vital patient interest of reaping the benefits of collaborating with others.

Conflict of interest statement

The authors declare that there are no conflicts of interests.

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