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Little to lose and no other options: Ethical issues in efforts to facilitate expanded access to investigational drugs

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ABSTRACT

Background: Today, public and private bodies around the world are trying to facilitate and increase expanded access to unapproved, investigational drugs for patients with unmet medical needs.
Methods: This paper discusses three major shifts in the field of expanded access and presents an argumentative account of ethical issues connected with those shifts, based on a literature study and unstructured interviews with 35 stakeholders in the Netherlands.
Results and discussion: Traditionally, expanded access has been based on three key principles: 1) it is exceptional, 2) it is done 'out of compassion', and 3) it has a *therapeutic* aim. Current efforts to facilitate expanded access affect these key principles, rendering expanded access a default option, allowing companies to charge for investigational drugs and gather data on its outcomes. These shifts may generate new ethical issues, including false hope, safety concerns and funding issues, which must be anticipated by physicians, pharmaceutical companies, payers and policymakers.
Conclusion: Healthcare systems allow for the use of promising unapproved drugs in exceptional circumstances, but do not always assist patients with unmet medical needs in getting access. It is time to replace the current patchwork of practices with systems for expanded access in which criteria are clearly described, responsibilities are assigned and arrangements are made, so that patients will know what (not) to expect from expanded access.

1. Introduction

When patients who are suffering from a serious or life-threatening illness have exhausted standard treatment options and cannot enroll in a clinical trial, they may be eligible for expanded access to unapproved, investigational drugs. These patients do not have the time to wait for marketing authorization of the drug, and may not meet inclusion criteria of available clinical trials (if there are any). Expanded access programs are intended for terminally or seriously ill patients for whom investigational drugs often represent one last chance at therapeutic benefit or survival. Many developed-world countries, including European countries and the USA, allow for expanded access to investigational drugs through so-called named-patient or compassionate use programs (see Box 1), which take place largely under the responsibility of the treating physician [1,2]. The treating physician must be convinced, based on the available evidence – which is limited, by definition – that for the individual patient, the potential benefits of trying the unapproved drug will outweigh the risks. Requsests for expanded access are commonly evaluated by health care authorities, which may approve the use of investigational drugs only when all authorized treatment options have been tried and failed. The explicit informed consent of the patient is required.

In current systems for expanded access, investigational drugs will only be supplied when all parties participate: the treating physician, the pharmaceutical company, the health care authority and/or institutional review board, sometimes a (hospital-based) pharmacist. Any one of these entities can unilaterally prevent expanded access from happening, sometimes because of a possible negative benefit/risk balance, or of lack of know-how, administrative burden, liability concerns or financial constraints.

In recent years, public and private organisations have started to claim that named-patient and compassionate use programs have been underemployed, and have taken action to remove barriers to expanded access to investigational drugs. For instance, the

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Box 1: Current systems of expanded access: compassionate use and named-patient programs.
Most developed-world healthcare systems (including European Union member states, the USA) have routes in place for expanded access to unapproved drugs. Although programs for expanded access vary across countries, most programs have the following key characteristics in common:
Key conditions:

- patients must suffer from serious and/or life-threatening diseases
- standard, approved treatment options have been exhausted
- there must be a reasonable benefit-risk ratio
- expanded access must not interfere with inclusion in clinical trials
- approval from a regulatory body is required

A patient trying to gain access to an investigational drug is dependent on all parties involved, including the physician, pharmaceutical company, health care authority, and sometimes, the institutional review board or (hospital-based) pharmacist, to cooperate. Any one of these parties can prevent expanded access from taking place. Roughly, there are two routes for expanded access: compassionate use and named-patient programs. For a more detailed explanation of these routes, see Appendix 1.

Goldwater Institute-driven Right-to-Try movement in the USA has campaigned to give terminally ill patients a legal right to access investigational treatments that have passed phase I testing, without having to ask for Food and Drug Administration (FDA) approval. By the end of 2017, Right-to-Try laws have been enacted in 38 American states [3,4]. In May 2018, a federal Right-to-Try bill was signed into law, which may shield physicians from professional negligence actions and bypass the FDA, but has been criticized for failing to compel companies to supply the drug or to make arrangements for funding. Consequently, few patients seem to have been able to gain access to investigational drugs through Right-to-Try laws [5–9]. In a series of highly publicized cases of seriously ill young patients, patients' families initiated social media campaigns to pressure pharmaceutical companies into releasing investigational treatments or to raise funds [10–14]. In Europe, the societal debate on expanded access has just got started, fuelled by initiatives such as adaptive pathways at the European Medicines Agency (EMA) [15] or the Early Access to Medicines Scheme in the UK [16], and the rise of commercial service providers such as myTomorrows [17] in the Netherlands or Clinigen [18] in the UK, which facilitate access to investigational drugs. While companies like Clinigen assist pharmaceutical companies in setting up compassionate use or so-called 'managed access' programs, myTomorrows targets patients and physicians directly, offering information about investigational drugs, managing requests for named-patient use, and arranging the licensing, import and distribution of the drugs. Efforts such as myTomorrows [17] and Orphanet [19] aim at helping patients with unmet medical needs navigate existing possibilities for access to investigational drugs. It should be noted that very little is known about the clinical benefits of expanded access programs for patients.

We contend that expanded access has traditionally been based on three key principles: 1) it is exceptional, 2) it is done 'out of compassion', and 3) it has a therapeutic, not a research aim. Recent efforts to facilitate expanded access, we observe, may instigate a shifting of these three principles. This article discusses each of these shifts, and points out some of their ethical and societal implications for patients, physicians and other stakeholders.

2. Methods

This paper aims to make a conceptual contribution to ethical and policy discussions of recent efforts to facilitate expanded access. It identifies shifts in three key principles of expanded access and the implications of these shifts for various stakeholder groups, including patients, physicians and pharmaceutical companies. In doing so, it builds on observations made through a study of the popular and scientific literature on expanded access and interviews with experts and stakeholders.

Literature was found by searching for terms as 'compassionate use', 'pre-approval access', 'early access', and 'named-patient programs' in PubMed or Embase and searching the references lists of the papers thus collected, through the Working Group on Compassionate Use and Pre-Approval Access (CUPA) at the NYU Langone Medical Center, in newspapers and online magazines and on websites from regulatory authorities, pharmaceutical companies, and non-profit organizations in various countries.

Semi-structured and unstructured interviews with 35 stakeholders in the Netherlands were conducted. Interviews were conducted with representatives from patient organisations (n = 4), physicians' associations (n = 3), health insurers (n = 3), hospital-based pharmacists (n = 3), biotechnology and pharmaceutical companies (n = 4), the Dutch Health Inspectorate, which oversees the safety and quality of health care (n = 2), the Dutch Medicines Evaluation Board, the drug regulatory authority that grants marketing authorisation (n = 3), the National Health Care Institute, the Dutch HTA agency (n = 2), policy-makers at the Ministry of Health, Welfare and Sport (n = 3) and experts from academia (n = 8, where n refers to number of interviewees). Interviewees from academia were among others experts in healthcare economics, innovation studies, and quality of life and end-of-life care. Interviewees were selected based on their positions in relevant organizations, on publications in the popular or scientific literature, and/or through snowball sampling. Interviews were conducted in 2015–2016, at the start of a research project titled 'Nice to meet? Meeting unmet medical needs: a social innovation to facilitate early access to investigational drugs', which was funded by the Dutch Organisation for Scientific Research (NWO). Short reports were made of each interview. The interviews were exploratory in nature and were used by the researchers to understand recent developments in the field of expanded access to investigational drugs and the views and experiences of important stakeholders.

The combination of a (non-systematic) review of the literature and interviews was used to establish the traditional criteria for expanded access and to reconstruct its key principles, to understand the implications of current efforts to facilitate expanded access for those principles on a theoretical level, as well as for important stakeholders on a practical-ethical level. Below we present an argumentative account of three major shifts in the landscape of expanded access and the ethical implications thereof.

3. Results and discussion

3.1. From an exception to a default option

Expanded access to investigational drugs has traditionally been granted "by way of exemption" [16,20]. It has been allowed only in the absence of other options, for patients "with a chronically or seriously debilitating disease, or a life threatening disease, and who cannot be treated satisfactorily by an authorized medicinal product," [20,21] and who do not meet the inclusion criteria of available clinical trials [22,23]. Though numbers are hard to come by, the uptake of expanded access seems low: fewer than 2000 requests are submitted annually in the USA (including large-scale,

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