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Pre-approval Access Terminology: A Cause for Confusion and a Danger to Patients

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Abstract

Background: Patients who are seriously ill and have run out of available treatment options may seek access to investigational agents that have not yet been fully vetted by regulatory agencies for safety and efficacy and approved for use in human subjects. Over time, a variety of terms have evolved internationally to denote mechanisms for providing access to such unapproved investigational agents. The lack of consistency in terminology used to describe this process is confusing at best and, at worst, possibly even detrimental to patients. *Methods:* To highlight variation around the globe in terminology denoting pre-approval access to investigational agents, we conducted extensive Internet searches to locate specific legislation, guidance, or policy documents describing access mechanisms in numerous countries. We created a table of results intended to convey a sampling of international terminological diversity. *Results:* The profusion of terms used internationally to indicate pre-approval access to investigational agents is evident. We recommend a shift toward the use of "pre-approval access" as an umbrella term encompassing all forms of access to unapproved agents. We also recommend use of the phrases "individual/named patient regulatory routes for pre-approval access" and "group/cohort regulatory routes for pre-approval access" to differentiate between pre-approval access programs designed for single patients, versus those designed for groups of patients. *Conclusions:* There is a pressing need to revisit and better align pre-approval access terminology at the international level. Adopting the umbrella term "pre-approval access" may be a useful strategy for initiating and promoting harmonization of terms to reduce potential confusion by patients and health care decision makers regarding experimental treatment options.

Keywords

compassionate use, expanded access, experimental drugs, global health, health policy

Introduction

Following several recent high-profile cases in the United States,[1,2] the process for seriously ill patients to obtain access to as-yet unapproved investigational agents outside of clinical trials has become highly scrutinized globally. There is great variation in the terminology used to denote policies and programs dealing with the issue of patient access to these unapproved drugs that are still in development.[3] Even within individual countries, terms are often used interchangeably or in ways that can be misleading. Based on several years of conversations with patient advocates, health care providers, regulatory staff, and members of the pharmaceutical industry, it is clear to us that this terminological inconsistency results in confusion and ambiguity, possibly with deleterious effects on patient health.

In the United States, the term "compassionate use" is often used to refer both to individual requests for access to investigational agents and to larger-scale, or group, access programs. Whether dealing with single patients or groups, the hallmarks of these programs are that they (1) deal with unapproved drugs and (2) their primary goal is to benefit patients therapeutically, rather than to collect data. However, these characteristics of pre-approval access programs are often misunderstood or lost completely in confusion stemming from use of the term "compassionate use." Focusing on the beneficial intentions of giving an experimental drug to a patient obscures the fact that anticipated benefits may be illusory; that the drugs may also cause harm; and that use of the drug in the patient who has no other options (and thus may be willing to gamble with regard to

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risks and benefits) may have implications for other patients and, indeed, for the continued development of the drug.

The phrase "compassionate use" has been used with regard to unapproved drugs since the mid-twentieth century; however, the phrase has an even longer history of use with marijuana used for medical purposes. The fact that this phrase is used in the contexts of both unapproved pharmaceuticals and medical marijuana has muddied the waters considerably, at least in the United States. Adding to the confusion, the Food and Drug Administration (FDA) uses the term "expanded access" instead of "compassionate use." Expanded access and compassionate use (in its pharmaceutical context) specifically refer to medical products that have not yet been approved by the FDA for sale or use; however, in our experience, patient advocates, providers, journalists, and others frequently confuse expanded access with "off-label" use, the use of an approved drug for an indication not stated on its FDA-approved label.

An Internet search for pre-approval programs around the world revealed a profusion of terms and program titles that vary considerably. Constructing a framework for equitable, international access to possibly life-saving drugs in development necessitates a clear vocabulary and conceptual clarity. We recommend replacing "compassionate use" and other nation-specific terminology with the term "pre-approval access" as an umbrella term for access to drugs that have not yet been approved by the relevant regulatory authority. Further, we suggest using the terms "individual/named patient regulatory routes for pre-approval access" and "group/cohort regulatory routes for pre-approval access" to better distinguish between pre-approval access mechanisms at the individual level and at the group (or cohort) level.

Background

Patients facing terminal illness or irreversible disease progression who exhaust all approved treatment options may seek to access unapproved agents still in development. These drug candidates may be at any stage of the drug development process. Ideally, patients would seek access to drugs for which safety and efficacy data are available (thus, in or after a phase II trial); however, patients have requested access to drug candidates that are as early in the development process as preclinical testing in animal or cell culture disease models.

Compassionate use programs in the US (also called early-access, expanded access, named patient, or single patient programs) began informally in the 1960s in response to concerns that the then-new FDA approval process interfered with timely patient access to possibly lifesaving medication.[4] The FDA published its first official early-access policy in 1979 in response to demand for experimental cancer drugs. However, the true catalyst that prompted formal compassionate use pathways came with the AIDS crisis of the 1980s. For the first time, organized patient groups demanded access to unapproved medications. In reaction, the FDA formalized Investigational New Drug (IND) applications in 1987 that allowed patients to obtain investigational drugs outside of clinical trials.[4,5] INDs were grouped into 3 categories: an "investigator" IND submitted by a physician conducting his or her own investigation of a drug; an "emergency" IND that allows the FDA to authorize use of experimental drugs in time-sensitive, emergency situations; and a "treatment" IND submitted for experimental drugs that show particular promise for serious or life-threatening conditions.[6]

In 1988, the FDA created an additional "fast-track" pathway that would expedite drug access for life-threatening conditions by omitting or deferring phase III clinical trials.[4,7] The drive for expedited access to experimental medicines and devices continued to grow into the 1990s as breast cancer advocates called for nontrial access to drugs in development.[8] In 1992, the FDA began its "accelerated-approval pathway," which allowed access based on reasonably likely patient benefits and softened the requirements of the clinical trial process by eliminating clinical end points (such as hospitalization and death) in favor of surrogate endpoints (such as lab values) that could be obtained in a shorter period of time.[9]

In 2009, after a lawsuit that unsuccessfully sought to establish an individual right to experimental drugs and resulting advocacy efforts that called for changes to FDA policies, the FDA revised its "expanded access" regulations, creating 3 categories or levels of access. These levels include access for individual patients (including emergency and nonemergency access), access for intermediate-size groups of patients, and access for large patient populations. Categories of expanded access are further subdivided into expanded access INDs (single-patient INDs, emergency IND, intermediate-size patient population IND, treatment IND) and expanded access protocols (single patient protocol; emergency protocol; intermediate-size patient population protocol; treatment protocol).[10] According to the FDA's published guidance documents, expanded access differs from the typical IND in that "expanded access uses are not primarily intended to obtain information about the safety or effectiveness of a drug."[11] Accordingly, unlike the extensive document that must be completed in order to obtain an IND, only several sections were required for those seeking to use an unapproved drug in development via expanded access. In 2015, after advocates widely (and incorrectly) claimed that filing paperwork for expanded access with the FDA routinely took 100 or more hours, the FDA removed the expanded access–related questions from the IND form and created a form (Form FDA 3926) specifically for expanded access requests, which the agency estimates takes approximately 45 minutes to complete.

As amply demonstrated by the US, even within a single country inconsistencies and ambiguity surround pre-approval access programs. Across the stakeholders of patients, industry, health care providers, patient advocates, and regulators there is no universally accepted definition for the terms "compassionate use" or "expanded access."[3,12] Rather, given the confusion caused by multiple terms, knowledge, and understanding of pre-approval access is elusive, with lawyers, regulatory experts, and even the FDA sometimes misusing or confusing terminology.

Table 1. Selected International Terms for Accessing Unapproved Agents.

Country	Program Name	Relevant Legislation	Associated Agency	Relevant Website(s)
Australia	Special Access Scheme Authorised Prescriber Scheme Named Patient Supply	Therapeutic Goods Act (1989)	Australian Government Department of Health Therapeutic Goods Administration	https://www.comlaw.gov.au/Series/C2004A03952 http://www.pharmaxis.com.au/named-patient-program
Brazil	Expanded Access Compassionate Use	Resolução da Diretoria Colegiada (RDC) 38/2013 (2013)	ANVISA (Brazilian Health Surveillance Agency)	http://www.sbppc.org.br/site/images/publicacoes/dou%20-%20resolu%E7%E3o%20rdc%2038_%20de%2012%20de%20agosto%20de%202013.pdf
Canada	Special Access Programme Future Use Request Notice of Compliance with Conditions Policy	Sections C.08.010 and C.08.011 of the *Food and Drugs Regulations (2015)* Sections C.08.004 and C.08.005 of the *Food and Drugs Regulations* (2015)	Health Canada	http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php
France	Temporary Authorization for Use (ATU) ATUc (cohort) ATUn (nominative/ named patient)	Code de la santé publique, Article L5121-12	French National Agency for Medicines and Health Products Safety (ANSM)	http://ansm.sante.fr
India	Procedures to Import Small Quantities of Drugs for Personal Use Named Patient Program	Drugs and Cosmetics Rules (1945)	Central Drugs Standard Control Organization	http://cdsco.nic.in/forms/list.aspx?lid=1852&Id=30
Israel	Compassionate Care	Pharmacists Ordinance (1981)	Israel Ministry of Health	http://www.health.gov.il/Laws/Pages/LegislationPage.aspx
Japan	Conditional Approval for Regenerative Medicines	Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (2014)	Pharmaceuticals and Medical Devices Agency	http://www.mhlw.go.jp/topics/bukyoku/soumu/houritu/dl/183-55.pdf http://www.sciencedirect.com/science/article/pii/S1934590915001230X
South Africa	Compassionate Use Clinical Access Programme	Section 21 of Act 101 (1965)	National Department of Health	http://www.acts.co.za/medicines-and-related-substances-control-act-1965/ http://www.scielo.org.za/scielo.php?pid=S0256-95742014000300012&script=sci_arttext
South Korea	Treatment Use of an Investigational New Drug Emergency Use of an Investigational New Drug	Notification 2002-65	Korean Food and Drug Administration	http://www.asiacroalliance.com/pdf/KFDAguidelines.pdf
Turkey	Compassionate Use	Guidelines for Compassionate Use for Humanity (2009)	Ministry of Health of Turkey General Directorate of Pharmaceuticals and Pharmacy	http://www.titck.gov.tr/ http://onlinelibrary.wiley.com/doi/10.1111/j.1759-8893.2012.00090.x/full
United Kingdom	Early Access to Medicines Scheme (EAMS)		Medicines and Healthcare Products Regulatory Agency	https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams#eams-public-assessment-report-par
United States	Compassionate Use Expanded Access for Individual Patients Expanded access for intermediate-size patient populations Expanded access for widespread treatment use	Code of Federal Regulations (21 CFR Part 312.300)	Food and Drug Administration	http://www.gpo.gov/fdsys/pkg/CFR-2012-title21-vol5/xml/CFR-2012-title21-vol5-part312-subpartI.xml http://www.fda.gov/ForPatients/Other/ExpandedAccess/ucm20041768.htm

Aside from the problems caused by this multiplicity of terms, there are flaws inherent in the terms themselves. For instance, the term "compassionate use" seems to depict a situation in which the compassionate option would be to give the investigational agent; however, when contemplating the use of an investigational drug that could help the patient but could just as likely cause harm, such simplicity is, unfortunately, neither realistic nor helpful and may imply a promise of therapeutic efficacy. Furthermore, while the phrase "compassionate use" has been used with regard to unapproved drugs since the mid-twentieth century, it has an even longer history of use in relation to marijuana used for medical purposes. The fact that this phrase, historically and currently, is used in the contexts of both unapproved pharmaceuticals and medical marijuana has muddied the waters considerably, at least in the United States. An Internet search for "compassionate use" turns up a confusing mix of results dealing with both medical marijuana and access to unapproved pharmaceutical products. Patients or providers seeking guidance can be derailed: for example, the Florida Department of Health's Office of Compassionate Use deals solely with medical marijuana, not access to unapproved drugs or other medical products.

"Expanded access," likewise, is a problematic term, not because it biases decision making but because of its vagueness. While "expanded access" specifically refers to medical products that have not yet been approved by the FDA for sale or use, in our experience patient advocates, providers, journalists, and others frequently confuse expanded access with "off-label" use, the use of an approved drug in a way not stated on its FDA-approved label (eg, using a drug approved only as an antidepressant as a treatment for nerve pain, using a medication approved for adult patients in a pediatric population, etc). This confusion is deepened by the fact that when the FDA approves an approved drug to be used for the treatment of additional conditions or in additional populations, this is deemed an "expanded use." Internet searches for expanded access often turn up results for expanded use and vice versa.

International Landscape: Overview of Pre-approval Access Terms

Internationally, countries establish their own pre-approval access guidelines and apply their own definitions and terms. This has led to a variety of programs globally that use similar, but rarely the same, terminology.[3,12] Further adding to the confusion is the difference between "expanded access requests" and "expanded access programs (EAPs)," the latter being more akin to a clinical trial in that, while the primary intent remains therapeutic benefit, EAPs involve both inclusion and exclusion criteria and some level of data collection.

Methods

We conducted initial Internet searches that occasionally pointed in the direction of a primary, government-published source or website. More often, the initial search resulted in the name of a particular act or ordinance, which was then tracked down through a nation's legislative body. Many search engine hits led to outdated legislation, a concerning trend in a globalized environment where patients in any country who might wish to appeal for access can learn of promising drugs in development domestically or internationally. Internet searches performed on the websites of various health ministries were frequently unproductive.

Results

Table 1 presents the great variety of terms used internationally to denote pre-approval access. The list of countries is not meant to be exhaustive; rather, the table is intended to illustrate the diversity of terms currently used to refer to the process for obtaining access to drugs in development before they are granted regulatory approval or, in some cases, after they are approved but before they are available to the public.

Several nations, such as Canada and Sweden, have consolidated information regarding their national approach to pre-approval access and have forms relevant to both individual patients and practitioners on government-sponsored websites. Other nations take a more decentralized approach, with information available on the webpages of individual drug manufacturers. Some nations, such as China, appear to have no policies on pre-approval access.

The terms themselves run the gamut from succinct ("Compassionate Use") to verbose ("Procedures to Import Small Quantities of Drugs for Personal Use"), with connotations ranging from neutral ("drug undergoing clinical trial") to less so ("unauthorized use of finished drug").

Discussion

Why Is the Proliferation of Terms Problematic?

Table 1 depicts the range of variation. This profusion of terms can lead to ambiguity and confusion, particularly in the international context (T. Watson, BSc (Hons), written communication, November 2016).[13] It is reasonable to believe that the abundance of terms has repercussions for both patients and physicians seeking to make treatment decisions. In the context of serious or terminal illness, issues around health literacy, decision-making capacity and informed consent, and physician-patient communication about care are paramount.[14-18] Ambiguous terminology may also hamper physicians' ability to interface with sponsors and with national regulators when endeavoring to advocate for a patient, as evidenced by the emergence of organizations designed specifically to handle these issues (T. Watson, personal communication, 2016).

Nearly half of all adults in the United States struggle with basic health literacy, with significant implications for communication, health care decision making, and health outcomes.[18,19] The health care system can be challenging to navigate for healthy individuals or for those with minor impairments. For individuals who are seriously or terminally ill,

confusion caused by the terms used to designate pre-approval options may critically impair meaningful, informed decisions about health care, particularly toward the end of life and during terminal illness: the context in which most pre-approval access requests originate.

Physician-patient communication is an important aspect of the pre-approval access process. In their role as clinical experts, physicians advocate on behalf of patients with pharmaceutical companies and with regulators: indeed, according to the Code of Federal Regulations §312.300,[20] most pharmaceutical companies specify that requests for unapproved drugs must come from the patient's physician.[21,22] As such, physicians become important gatekeepers with significant latitude to influence decision-making outcomes. Effective advocacy requires that physicians and patients both have a mutually clear understanding of the goals of treatment and the values underlying these goals, in addition to an understanding of the clinical information. Confusion regarding terminology in the context of pre-approval access could impair vital physician-patient communication.

This is, perhaps, especially relevant for those near the end of life. Patients incur disproportionately large medical expenditures at the end of life, and mainly on life-sustaining procedures.[23] However, greater expenditures do not equate to better quality of life outcomes.[23] In fact, high expenditure on medical care in the last week of life is associated with a lower quality of death.[24] Improved communication between patients and physicians at the end of life may correlate with reduced costs and better outcomes.[24-26] If this is, indeed, the case, then ambiguous terminology that hampers physician-patient communication about pre-approval access to experimental treatments may ultimately result in poorer health/quality of death, or shortened lives.

In the context of communication throughout the pre-approval request process, communication between physicians and drug manufacturers and between physicians and regulators may also be compromised by a lack of clarity around pre-approval terminology (T. Watson, personal communication, 2016). This contributes further to a lack of equity in the process. Patients fortunate enough to have doctors familiar with the process and its associated terms are far more likely to gain access to experimental treatments than those whose doctors are unaware of the options or not as adept at navigating the process.[27]

Sponsors also struggle to understand and work within the landscape as a result of terminological confusion.[13] In fact, the issue is so pressing that some pharmaceutical and biotechnology companies are now outsourcing their pre-approval access activities to specialist providers who have developed expertise in navigating both the terminological and regulatory differences within and between countries (T. Watson, personal communication, 2016). The fact that such entities exist speaks volumes to the difficulty in parsing through lexical and regulatory variation. Again, those in a position to be aware of such services and seek them out are at a distinct advantage.

Building on the above example, implicit recognition that seeking pre-approval access is confusing for both patients and physicians is evident in the recent burst of activity regarding "navigators." Non-profit pediatric cancer charity Kids v Cancer created a navigator service in which an expert walks patients or providers through the request process. Moreover, the US FDA has publicly contemplated creating a navigator search to help patients and physicians with expanded access requests.

Finally, in addition to the role that physicians typically play in seeking pre-approval access for patients, patient advocacy organizations also may be involved, working on behalf of patients. As Andrew McFadyen, Founder and Executive Director of the Isaac Foundation, notes, "For patients and advocates, it's difficult to find their way through these systems, it's difficult to know that Expanded Access means Compassionate Use, and that both mean access outside of the investigational setting. Terminology is important, and would have saved us a lot of time as we connected with both the FDA and the company." (written communication, November 29, 2016). In discussing a particular case in which he and his organization advocated on behalf of a patient suffering from Hunter Syndrome (MPS II) whose parents were seeking access for their son to a drug via pre-approval access (initially in Phase I/II clinical trial testing, now in Phase II/III), McFadyen pointed with urgency to the fact that they did not have a moment to spare as the patient's condition continued to decline, and that confusion around terminology cost them precious time as he endeavored to navigate his way through the request process (personal communication, November 29, 2016).

Public interest in pre-approval access appears to be increasing, based on reports from pharmaceutical companies, on the FDA's reports of expanded access approvals, and on an increase in relevant petitions showing up on websites such as Change.org. Yet increasing interest, unless coupled with an easier-to-understand process or education, is likely only to lead to increasing confusion and frustration among those trying to gain access to investigational drugs. Thus, despite the inevitable frustrations that accompany a shift in terminology, we call upon all stakeholders to adopt standard language.

Which Term Is Best?

The term "compassionate use" is confusing and inherently subjective and value-laden. If an investigational agent is sought on "compassionate" grounds, a manufacturer who denies a request is acting, by definition, without compassion—a situation that does not square with reality. Drug manufacturers must make extraordinarily difficult decisions about whether to provide access to an unapproved agent. Declining a request may be rooted in trying to protect the patient from additional suffering or hastened death.[27] Alternatively, declining a patient's request may express compassion for the multitude of patients, both present and future, waiting to reap the benefits of a fully tested drug in development, given that in certain circumstances serious adverse events in the sort of seriously ill patients that would

seek to try an investigational drug outside of a clinical trial may slow or halt the development of the investigational agent.[28] Likewise, under-enrollment in clinical trials as a result of patients opting to access the drug outside of the trial would slow the new drug's approval timeline and, hence, the date it becomes available to all patients.

Furthermore, the term "compassionate use" can be interpreted to mean that an investigational agent will be given free of charge, which is not the case in several countries. Additionally—at least in the United States—"compassionate use" is used to denote the medicinal use of products such as marijuana that are not part of an FDA-regulated drug development program. For all these reasons, it is inappropriate to link compassion with access decisions, making compassionate use a problematic term that ought be abandoned despite its historical usage and inherent appeal.

The term "expanded access," likewise, is not ideal. "Expanded access" is the FDA's umbrella term for pre-approval access to investigational drugs; however, it is a vague term. Whatever "expanded access" might be understood as meaning, it is doubtful that this term conveys, especially to those not familiar with drug development, that the drug is still experimental and has not yet been approved for sale or use in patients outside of clinical trials. Furthermore, this term is very similar to "expanded use," which refers to an approved drug being approved for uses beyond those of its original approval. Confusion between expanded access and expanded use is analogous to conflation of the terms "compassionate use" and "off-label use." As long as a drug is approved by the FDA for sale and use, physicians may use that drug as they wish (within bounds that would be considered reasonable by other physicians) be it for conditions other than those indicated on the drug's label or at a dosage or frequency other than those specified by the label. A physician's decision to use an approved drug "off-label" may well be based in compassion, but this is not what is meant by the term "compassionate use"—nor the term "expanded access."

Recommendation for Change

As a result of the proliferation of terms that have evolved over time and the diverse international laws, policies, and programs that offer access to experimental treatments, efforts to unify terminology for greater clarity and consistency face an uphill battle. Harmonization of terms will require compromise on terms that many countries or agencies may be reluctant to modify. While some multiplicity of terminology is necessary to encompass the varied goals of policies and programs, a few small-scale changes may provide a feasible starting point for incremental change. The aforementioned examples demonstrate confusion faced by patients, physicians, sponsors, and patient advocates due to terminological inconsistency and complexity. Initial small-scale changes can create value by reducing difficulty and frustration for all stakeholders, not to mention helping to avoid potential negative repercussions for very ill patients.

Pre-approval access

We suggest use of the term "pre-approval access" as an umbrella term to describe any form of access to an investigational treatment prior to completion of the formal testing and approval process. Though "compassionate use" may seem an appealing and accurate term, it is not suitable to describe access to as-yet unapproved medicinal products for the reasons articulated above. "Expanded access" is too vague a term to be descriptively useful and so similar to "expanded use" as to cause confusion. Thus, we call for adoption of the new, value-neutral, self-explanatory term "pre-approval access."

Individual/named patient regulatory routes for access and group/cohort regulatory routes for access

To further reduce the confusion around pre-approval access mechanisms for individuals versus for groups or cohorts, we suggest the terms "*individual/named patient regulatory routes for access*" for pre-approval access on an individual basis and "*group/cohort regulatory routes for access*" to describe pre-approval access programs at the collective or group level. These terms harmonize with much of the terminology currently in use internationally and may help to mitigate terminological ambiguity confounding the pre-approval access process for desperately ill individuals. Furthermore, by eliminating the FDA's current distinction between intermediate-sized and treatment protocols, investigators will no longer have to seek regulatory guidance about whether their group/cohort program is deemed to be intermediated sized or a treatment program.

Conclusions

The evolution of compassionate use and pre-approval access over time has resulted in linguistic ambiguity stemming from different regulatory environments and different policies within individual nations around the world. In order to unify and improve equitable access to unapproved treatments, it is advisable to establish a universally accepted lexicon with which to discuss pre-approval access. While this will necessitate modifying policies and regulations, we believe the benefits of harmonization will be significant enough to warrant such efforts. We believe consistent use of the umbrella term "pre-approval access" to denote patient access to investigational treatments prior to formal approval, and use of the terms "individual/named patient regulatory routes for access" and "group/cohort regulatory routes for access" to differentiate pre-approval access at the individual or group level represent an important and implementable step in the overarching goal of creating a transparent, clear process for seeking and providing access to unapproved, potentially life-saving agents.

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