Post-Trial Access to Treatment

Corporate best practices

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Medicines for the European market are increasingly being tested on clinical trial participants in low- and middle-income countries, where most participants are poor and have limited access to health care. Against this backdrop, the right to Post-Trial Access to Treatment (PTA) after the trial has ended becomes increasingly important to avoid the exploitation of vulnerable participants. The problem is that patients are being enrolled onto clinical trials in the full knowledge of the trial sponsors that they will not have access to the continuing treatment they may need once the trial has finished. This practice is unethical.

> *"Because I will get into this trial, I get better, and then afterwards I am going to die. You have promised me life and then you take it back; that's not fair."*
>
> *HIV/AIDS Clinical Trial Participant, Kenya 2006*

The Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),[1] which has been integrated into European legislation,[2] comprehensively describe the responsibilities and expectations of those involved in the conduct of clinical trials. However, these guidelines do not describe any responsibilities for continuing treatment after the trial.

Leading international ethical guidelines such as the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) guidelines include the right to PTA, but these are not consistent and still raise many questions. This lack of firm guidance is fuelling a heated academic debate about fundamental ethical questions regarding the treatment of patients after clinical trials.

> *"In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process."*
>
> *(Article 34, Declaration of Helsinki 2013)*

In the midst of this ethical and theoretical minefield, what happens in practice? How do pharmaceutical companies deal with this complex issue with little practical guidance and without binding regulations? There is a big gap in our knowledge about how the pharmaceutical industry currently deals with PTA in practice. The objective of this research is to address this gap by offering a collection of PTA practices in low- and middle-income countries, as provided by the pharmaceutical industry.

The Centre for Research on Multinational Corporations (SOMO) approached a number of the biggest pharmaceutical companies asking for a good example of a real situation in which they arranged and financed the continuation of treatment after the completion of a trial in a low- or middle-income country – in other words, we were looking for examples of best practice.

It should be noted that this paper does not aim to critically analyse the PTA practices provided by the companies or to expose unethical practices – not least because there is currently no widely accepted PTA standard with which to compare these practices. The ambition of this paper is to help define a high yet realistic standard of PTA in low- and middle-income countries, one that overcomes the ambiguity of the current guidelines and that is acceptable for the industry and civil society organisations alike.

The underlying assumption in this paper is that identifying the common elements of company best practice will help to put standards in place: by identifying current best practices, the expectation is that companies operating below these levels will aim to raise their own standards to at least this level.

> *Expert: "There is no consensus on what a PTA best practice should look like. My personal opinion is that if you don't have an alternative treatment, then you should continue with the experimental drug. But if there is an available treatment, then you should go back to that drug until the regulatory authority approves the drug. So there is not one recipe."*

Problem description

While all the phases of a clinical trial are highly regulated, including the stage prior to the actual beginning of the trial (informed consent process), what happens right after the trial is not regulated.

In theory, pharmaceutical companies seem to accept a certain degree of responsibility regarding the provision of PTA. However, in practice PTA appears to be rarely provided in LMICs, where the need for PTA is the greatest. Since the national health-care systems in LMICs are often not able to provide follow-up treatment after the trial, the situation may occur that patients who have received treatment through their participation in a trial fall back on the local standard of care once the trial is completed. This can result in the unwanted situation of the cessation of a beneficial treatment.

We acknowledge that addressing PTA might be secondary to the very fundamental issue of universal access to health care and life-saving medicines. If access to health care and life-saving medicines were secured world-wide, the lobby for post-study obligations would become redundant.[3]

Methodology

This research focuses on nine of the 20 pharmaceutical companies that ranked highest by revenue in 2013 (see the table on the next page). The sample of the companies analysed in this paper has been influenced by the degree of difficulty in identifying and gaining access to relevant people within the companies. The selection is therefore linked to the degree of accessibility and responsiveness of the companies on the subject of PTA. The findings are not representative for the whole sector. However, since we want to highlight the most advanced company policies on PTA, our assumption is that they are likely to be obtained from the most responsive companies on the subject.

> *Company: "I supervise the department that manages clinical trials, so I don't know anything about the post-trial phase. For this point you need to contact our global head quarter."*

Nine companies provided answers about their PTA policies and practices by email, and five of them agreed to a phone interview. SOMO asked for examples of PTA provided after a clinical trial in a low- or middle-income country, solely sponsored by the company.[4] The requested examples were supposed to represent a good example of what the company considers to be in line with the international ethical guidelines they endorse. Not all the companies were willing or able to share examples of PTA matching SOMO's request, due to the fact that they do not keep records on PTA, or the information is not for public consumption, or simply because PTA is not provided by the company in a low- or middle-income country (LMIC) as far as the contact person was aware. All companies are given the opportunity to review their quotes and the presentation of their PTA examples.

Alongside the search for corporate best practice, SOMO analysed the company policies on PTA, the strong and weak points of international guidelines, and reviewed part of the academic debate, without the goal of contributing to this debate.

Rank (by revenue 2013)	Companies participating in the research	Interview	Answers by email	Provided examples of good PTA practice in LMIC
1.	Novartis	No	Yes	1
2.	Pfizer	No	Yes	
3.	Roche	No	Yes	
4.	Sanofi	Yes	Yes	6
6.	GlaxoSmithKline (GSK)	Yes	Yes	1
8.	AstraZeneca	Yes	Yes	1
9.	Eli Lilly	Yes	Yes	
13.	Bayer	No	Yes	
18.	Gilead	Yes	Yes	1[5]

Source: IMS Health, based on revenue 2013.[6]

Reading guidance to the briefing paper

Although the literature on the subject of PTA is quite vast, practical examples are poorly documented, both in the literature and on the internet. This research aims to fill that gap. Starting from a review of the current international guidelines and of the main streams of academic production on the topic, it will then offer a reflection on the most advanced company policies on PTA. Examples of what companies indicated as their best PTA practice will follow. On the basis of these reviews and practices, this paper will then draw some conclusions and suggest elements for a realistic high-level standard of PTA. Finally, some recommendations for implementation of such standards will also be given.

PTA in the international ethical guidelines

We have indicated that it is a problem that international ethical guidelines are not aligned. However, existing guidelines do contain strong elements that, individually, could offer enough grounds for more harmonised PTA policies. The review on the next page highlights the strongest characteristics of each set of guidelines in order to identify what can be considered essential for PTA good practice.

PTA in legislation

Brazil is the only country where there are currently binding regulations to provide PTA (see Box 1). In a few LMICS, such as Uganda, India, South Africa[7] and Argentina,[8] non-binding national guidelines support the provision of PTA. However, these are not mandatory.

Argentina will have a law that refers to PTA as soon as the new Civil and Commercial Code comes into force from January 2016. Although the language remains vague,[9] this is another rare example of PTA obligations incorporated in national laws.

PTA in the academic debate

Issues around PTA range from medical science, bioethics, human rights, law and politics to economics and marketing. As a result of this complexity, a vast array of academic resources is available to deal with the medical needs and ethical, moral, political, legal and practical dilemmas.

For this paper, two main streams of debate are particularly relevant. The first stream of academic literature deals with the fundamental question about the general desirability of PTA; arguments in favour and against PTA are widely discussed. In the second stream of debate, academics discuss the ethical implications of what appears to be the most pragmatic way to provide PTA with an unlicensed drug: Open Label Extension Studies[10].

A fundamental question: is PTA always desirable?

The principle of non-malfeasance (do no harm) is undisputed in medicine, and most arguments in favour of PTA refer to it. A drug that has proven to be beneficial to someone cannot be withdrawn. Moreover, when it comes to LMICs, the principles of justice and global ethical standards are evoked and contribute to an increasing consensus on the desirability of PTA.

International ethical guidelines – strong elements

2013 Declaration of Helsinki,[11] **article 22:**
"In clinical trials, *the protocol* must also describe appropriate arrangements for post-trial provisions."

2013 Declaration of Helsinki, article 34:[12]
"In *advance* of a clinical trial, *sponsors, researchers and host country governments* should make provisions for post-trial access for *all participants who still need an intervention identified as beneficial in the trial.* This information must also be disclosed to participants during the *informed consent process.*"

CIOMS/WHO Guidelines, guideline 5:[13]
"*Before requesting an individual's consent* to participate in research, the investigator must provide [the research subjects] the following information [...] *whether, when and how* any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and *whether they will be expected to pay for them.*"

CIOMS/WHO Guidelines, guideline 10:[14]
"Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that: […] any intervention or product developed, or knowledge generated, will be made *reasonably available* for the benefit of *that population or community.*"

CIOMS/WHO Guidelines, commentary to guideline 10:[15] "If an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to *the subjects after the conclusion of the study,* and pending its approval by a drug regulatory authority."

Nuffield Council on Bioethics:[16] "We therefore endorse the NBAC recommendation that researchers should endeavour *before the initiation* of a trial to secure post-trial access *for effective interventions for participants in the trial* and that *the lack of such arrangements should have to be justified* to a research ethics committee."

Recap of the strong elements in the guidelines

- Importance of *advanced planning* of any provisions of PTA (Declaration of Helsinki – DoH, Nuffield Council, CIOMS/World Health Organization – WHO).
- PTA provisions should be described in advance both in the *clinical trial protocol* (DoH) as well as in the *informed consent forms* (DoH, CIOMS/WHO).
- *Allocation of specific responsibilities* to actors involved in the trial and post-trial phase should be clear prior to the trial (DoH, Nuffield, CIOMS/WHO). *Financial responsibilities* in particular need to be clearly specified (CIOMS).
- PTA should be *ensured for all participants* in the trials (Nuffield, CIOMS/WHO), and undoubtedly for those who still need an intervention identified as beneficial (DoH).
- The intervention or product developed, or generated knowledge, should be made (reasonably) available, not only for trial participants, but also for the benefit of that *population or community* (CIOMS/WHO).
- *Effective interventions:* These may include but should not be limited to the investigational drug (Nuffield). It is important to recall here that, although no longer en force, the 2008 version[17] of the DoH mentioned that PTA was not limited to access to interventions identified as beneficial in the study, but it was extended to "other appropriate care or benefits".
- *Lack of PTA arrangements should be justified* to research ethics committees (Nuffield).

Related to this practice, academic experts argue that PTA may not always be desirable. During a meeting on PTA organised by SOMO and Wemos in June 2012,[18] experts voiced some of the common objections against the provision of PTA:

- PTA may cause undue inducement, since the expectation of follow-up care or any other benefit, especially in LMICs, may persuade people to participate in clinical research.[19, 20]
- PTA may delay trials because of procedures and agreements to be made with governments, sponsors, researchers and others involved.
- PTA may prevent trials from happening, since the financial burden of PTA provision may become a disincentive for sponsors to conduct clinical research, especially in LMICs.[21]
- PTA may be misused as a marketing tool, as in the case of Long Term Extension studies.[22]

Dainesi and Goldbaum stress that decision-making processes about PTA should take into account that PTA may not always be appropriate: "The decision must be submitted to at least two assessments: efficacy and safety of the new experimental drug".[23]

Zhiyong Zong highlights how much PTA is influenced by contextual circumstances. He claims that provision of PTA should be established "if need be". He says that, "Implementation of mandatory post-trial provision usually encounters many difficulties, but they may be tackled by careful advanced planning".[29]

Along with this larger stream of debate,[25, 26] Usharani and Naqvi identify a number of potential points to ponder before considering the provision of PTA: one of them is that giving the drug to trial participants while the rest of the population does not have access to it can create disparity, especially in low resource settings. Another point is the duration of PTA: the (un)feasibility for the sponsor to provide PTA for an unlimited period, especially for chronic diseases. Moreover, PTA with an investigational drug should be reconsidered when evidence is preliminary and exposure to that drug may still be hazardous. Usharani and Naqvi highlight the importance of addressing all these issues in the clinical trial protocol before regulatory and institutional approval. They argue that "providing alternative benefits is more feasible for sponsors and can be applied uniformly to all subjects rather than agreeing to post-trial access" [to the investigational drug].[27]

Alternative benefits may range from strategies to make medical drugs more affordable in developing countries[28] to benefits tailored to specific contexts and negotiated with communities when there is no opportunity of direct benefit from a specific intervention.[29]

Box 1: National regulations on PTA – the unique case of Brazil

In her interview with SOMO, Dr. Sonia Dainesi, a Brazilian leading expert in the field and author of studies on the topic of PTA, explained why Brazil is an exception in the area of PTA: "The national system is very good, because you have to provide PTA by law and you have to include the PTA provisions before the trial starts, except if the patients don't benefit of the drug or if the doctor thinks it's not necessary to continue with this drug".[30]

The first regulation that addressed access to unregistered drugs under expanded access programmes was the RDC 26/1999.[31] Recently, Brazil's Health Surveillance Agency issued a new regulation, RDC 38/2013,[32] which expands further the access to investigational drugs.

However, Dr. Dainesi explained the shortcomings: "Who is responsible for providing the drug is the problem. The legislation says that the sponsor is responsible for the provision of PTA, which is usually the industry, but not always. Sometimes it's the institutions, or the government, or the academia that conduct the studies."[33] However, the latter often do not have sufficient funds to grant the provision of PTA. The result is that the ethical duty of providing PTA and the legally enforceable right of receiving it are constantly regulated in courts: "Patients who participate in clinical trials can sue, with a high probability of success, either the pharmaceutical company or the State to force them to keep providing the experimental drug. This has triggered, in turn, further lawsuits in which either the state or the pharmaceutical company, when sued by the patient, sue each other trying to transfer the responsibility to provide the experimental treatment".[34]

The current legal conditions described here contribute to making Brazil a very unique case as far as the provision of PTA is concerned. Participants have the right to PTA as part of their right to health care, but the duty of providing it is often decided through litigation.

In reference to the concept of "benefits", some scholars critique the formulation of paragraph 34 in the new version of the Declaration of Helsinki. The recent exchange of opinions between Del Re and collaborators[35] and Mastroleo[36] demonstrate how definitions of "benefits" or "other appropriate care", which were lost in the 2013 version of the Declaration of Helsinki, are still discussed. The matter is not semantic but rather substantive, as it relates to a fair distribution of benefits of clinical research.

The debate on pragmatic choices

Whilst the primary goal of clinical research is to contribute to scientific knowledge, the provision of health care is based on the ethical principles of treating patients and possibly saving their lives. The common practice of 'Open Label Extension Studies' as a pragmatic way to provide PTA with unlicensed drugs results in blurring the lines between research and health-care provisions, which are fundamentally and practically regulated by different ethical principles. This has prompted a stream of debate among scholars.[37, 38, 39, 40] The issue is concisely expressed by the question Cho gives to her paper: "Open-Label Extension Studies: are they really research?".[41] Authors discussing this topic point to the ethical dilemma of using clinical research to provide health care. While research has the ultimate objective of generating scientific knowledge, the goal of health care is to provide health to individuals. This may not coincide with the balance of risks/benefits for a clinical trial where in principle individuals volunteer to serve research purposes.

As well as raising the ambiguity between care and research, Open Label Extension (OLE) studies also blur the lines between PTA and marketing. Taylor and Wainwright published an article that also summarizes the ethical dilemma in its title: "Open Label Extension studies: research or marketing? Who is benefiting the most out of it: the patients or the companies?"[42] PTA within the context of an OLE raises the question whether the company is doing this out of compassion or just because it still needs data on the long-term safety and tolerability of the investigational drug for the marketing applications.

PTA in the companies' policies and practices

Since many aspects of PTA are still being debated and international ethical standards provide little guidance regarding what responsibilities a commercial sponsor must take and how, pharmaceutical companies are adopting a pragmatic approach towards the problem of conducting trials among vulnerable or underprivileged populations. Some common practices emerge from the analysis of the policies published by the companies that collaborated with this research and the statements given by the companies' representatives in their interviews with SOMO.

Commitments to PTA

Clear company commitments in reference to the right to PTA are not abundant. There was one clear statement on Novo Nordisk's website: "Clinical trial participants should have access to best proven and available treatment after a trial has stopped".[43] Although not sufficiently discussed, PTA is mentioned in various company policy documents which contain information about the post-trial care for clinical trial participants. All nine companies analysed for this research have included the Declaration of Helsinki (DoH) in policy documents on their websites. Either as a reference instrument for human rights (Sanofi[44]) or as an international ethical guideline the company "follows" (GSK[45]) or "adheres to" (Gilead,[46] Eli Lilly,[47] Novartis[48]) or "complies with" (AstraZeneca,[49] Pfizer[50]), or operates "in accordance with" (Bayer[51]), or "in full conformance" (Roche[52]). Including the DoH unreservedly can be seen as a commitment by companies to acknowledge the right to PTA.

Disclosure of PTA provisions

The addition to article 34 in the 2013 version of the Declaration of Helsinki (DoH) says that PTA provisions must be disclosed to the participants during the informed consent process. This is actually already part of some of the company policies:

> ***Roche**: "Before commencing a Roche sponsored clinical trial in a low or middle income developing country, Roche will ensure that a description of post-trial drug supply is written and incorporated into the protocol and patient informed consent forms."[53]*
>
> *Another example of this is from **Sanofi**: "The issue of PTA is always addressed in the study protocol and in the patient information documents which are used for soliciting informed consent."[54] For Sanofi, addressing PTA also means that if it is clear that no post-trial treatment will be provided, patients will be informed beforehand, and the protocol will indicate the rationale for this.[55]*

The practice of these policy statements cannot be verified by SOMO because complete clinical trial protocols and informed consent forms are not made public. Protocol summaries in clinical trial registries such as ClinicalTrials.gov[56] do not include a field for the PTA provisions. Also the 'WHO Data Set', which defines the minimum amount of trial information that must appear in a register in order for a given trial to be considered as fully registered, does not include the requirement to give information about PTA provisions.[57]

SOMO has been informed by Bayer that the company keeps a database of Managed Access Programs (MAP) (this definition is used as equivalent to PTA programmes by Bayer).[58] Bayer is the only company in this research that mentioned collecting this kind of information centrally in a database, but this is not made publicly available.[59]

In the absence of a standard definition of PTA, is there a standard practice?

Only in exceptional circumstances

Most of the companies included in this research are very clear that PTA will only be provided in very specific and exceptional circumstances, on a case-by-case basis. They indicate that under certain circumstances they may decide to provide PTA. Sanofi shared a part of an Internal Quality Document on Informed Consent recently validated by the internal Bioethics Committee. The document contains a certain number of principles, which are in the process of being integrated into operating procedures documents. The Internal Quality document's section on Post-Trial Access clarifies Sanofi's position in respect of the issue of post-trial access to investigational products, both in pre-approval studies and in post-marketing studies using locally licensed medicines. It reads: "Post-study access and participant follow-up arrangements can only be made on a disease-by-disease, compound-by-compound or study-by-study basis".[60]

The way GSK describes these circumstances in its policy summarises the various company positions very well: "There may be circumstances when there is a compelling medical rationale for patients who have derived a measurable medical benefit from an investigational compound during a clinical trial to continue to receive that compound (e.g. the illness being treated is life threatening or seriously debilitating and there are no other treatments available or there are significant risks in switching patients to alternative treatments). When this is the case, GSK may extend a study to facilitate appropriate continued access to the investigational product. Alternatively, the availability of an expanded access programme may serve as a means of continued access".[61]

If we summarise the information that is available in policies and that was obtained through interviews with companies, we see a standard practice emerging.

Companies consider providing PTA in case of *non-licensed medicines* until the medicines are approved and become licensed under the conditions that:

- The disease or condition being studied is serious or life threatening and/or long term.
- The patient is benefiting and discontinuation of treatment might adversely affect the patient's health or well-being.
- There is no (local) availability of alternative treatment.
- There is sufficient efficacy and safety data and a positive benefit-risk balance.[62]

Companies consider providing PTA in case of licensed medicines (i.e. with marketing authorisation in the country) when the four conditions occur and patients still do not have access to the medicines despite the license, as in the situation where national health care does not fund it. However, this is considered even more exceptional.

> ***AstraZeneca:*** *"If we decide to continue, then we make sure that it is up to the moment that the drug is authorized and we can bring the product in the market. And if we do a trial with a medicine that is already in the market, normally we will not provide further treatment. But even then, in certain exceptional circumstances, we can decide to provide them to the patients who don't have access to the medicine".*[63]

> ***Merck:*** *"In general, the provision of post-trial care for clinical trial participants continues under the applicable health care system of the host country."*[64]

> ***GSK confirms this:*** *"I think that most companies are very sympathetic to find a way to provide access when it's a disease where patients are at acute risk of death or sickness. But I guess the problem is that most drugs are offering a benefit but there are still other treatments available that could be used. So I suspect that in most circumstances, patients fall back on standard of care which may not have the new advantages of the new medicine but nonetheless provides some sort of reasonable cover".*[65]

The described nature of "exceptional circumstances" under which companies "may" (or may not) consider providing continued access to treatment after a clinical trial shows the freedom of the companies to make their own decisions about this because there are no binding regulations, except in Brazil. It also becomes clear that companies only consider PTA when the trial concerns a non-licensed drug. The provision of licensed drugs is seen as the responsibility of the government and national health-care systems. As Sanofi put it: "The company cannot replace the national health-care system".[66]

The preferred routes for PTA

The emerging standard practice for providing an unlicensed investigational drug until marketing approval is:

1. By enrolling the participants into a study extension (an Open Label Extension Study (OLE) or Long-Term Extension Study (LTE).
2. Through one of the forms of Early Access Programmes (EAP), depending on the national regulatory framework in place.

Related to point 2, in the United States, the Food and Drug Administration (FDA) regulation[67] allows access through "Expanded Access Programs", while EU regulation[68] allows such access through Compassionate Use Programmes (CUPs). There are Cohort CUPs (CUPs made available for groups of patients or hospitals on the basis of requests from physicians or companies[69]) and Named Patient CUPs (CUPs made available for individual patients on the basis of the physician's request[70]).

Characteristics of the most common PTA practices

Open Label Extension Studies (OLE) or Long-Term Extension studies (LTE)

Description: An extension of a clinical trial on the basis of a new study protocol in which the participant, health-care professional and others know the drug and dose being given (not blinded).

Aim: It is conducted to assess the long-term safety and tolerability of an Investigational New Drug but is also used for continued prescribing of unlicensed medicines after a randomised trial to patients with medical need of the investigational medicine.

Compassionate Use Programs (CUP) or Expanded Access Programmes (EAP)

Description: An early access programme is a way of making a promising medicine available to patients when it has not yet been authorized (licensed) for their condition.[71]

Aim: To make available unlicensed medicines on the basis of compassion but also used to provide a PTA. Compassionate Use Programs and Expanded Access Programs can be considered substantially equivalent on the basis of the following characteristics: a) the compassion-based drug provision; b) the drug is not yet authorized; c) no alternative therapy is available; and d) there is no research objective or study protocol involved.

__AstraZeneca__ describe their practice as follows: "If a decision is made to continue to provide a clinical study drug after the original study is completed, we will ensure that appropriate oversight measures are in place, such as dispensing treatment in the context of a clinical study or a compassionate use programme".[72]

Since __Gilead__ mostly engage in the production of HIV and AIDS drugs, the company confirmed their coherence with the Good Participatory Practice issued by UNAIDS in 2011, where it is stated that post-trial access should be provided in the form of "follow on, open label, or other such studies before product licensure or approval".[73] It follows that Gilead's way of allowing access to investigational drugs will be a Gilead sponsored protocol.

__Novartis__ say: "Where applicable, […] research participants may, after trial completion, be offered participation in an extension study until marketing authorization".[74]

Although considering Open Label Studies as their current standard, GSK seem to be in the process of considering a transition to a different practice. A spokesman said that, if an Open Label Study is based only on the ethical need to supply the drug to the trial participants who benefited from the drug, then the drug should be provided with more clinical freedom and without the limitations of clinical trial protocols and the requirements for clinical data collection. Therefore the company's standard may shift from an Open Label Study to an Expanded Access programme. GSK has produced a new protocol on this topic, which is expected to be rolled out soon.[75]

PTA in low- and middle-income countries (LMICs)

From what has already been discussed above, we can conclude that companies accept responsibility for PTA in principle but only under very specific and exceptional circumstances, on a case-by case basis and only until the investigational drug is licensed. The current shift of clinical trials to LMICs[76] means that pharmaceutical companies increasingly have to deal with poor patients with limited access to healthcare (i.e. vulnerable groups) in their trials. Dealing with groups that are defined as vulnerable by the international ethical guidelines[77, 78] makes PTA even more relevant for these countries.

In their policies and in their interviews, all companies confirm that they apply the same ethical principles globally. When ethical standards cannot be upheld or where the local standard of care is unacceptably low, the common solution seems to be that companies avoid conducting trials in those places altogether. "If local care would not be able to provide treatment follow up, then we would stop doing research in that site," as Gilead stated.[79] Some of the companies in this research stated that, before doing research in a LMIC, they will obtain assurance that the local health-care system will be able to provide continued care.

__GSK:__ "Responsibility for post-trial provision of nationally licensed medicines used during a trial lies with governments as part of national healthcare

programmes. For diseases/conditions that continue beyond the end of an interventional study, GSK-sponsored clinical trials will not be carried out unless we have assurance ***from the investigator*** *that subjects will receive, or be referred for, any necessary continued healthcare and that the healthcare system is able to provide for the continued care of trial participants."*[80]

Talking about unlicensed medicines, ***Sanofi*** *say: "We ask ourselves whether we are dealing with a population that qualifies as vulnerable. Our position is to exclude vulnerable populations from these clinical trials".*[81] *In relation to trials with licensed medicines in LMICs (but not limited to LMICs), Sanofi says that "participants will be included in a study only if they can indicate that they expect having, within the local healthcare system, access to continued care for their medical condition once they have completed their study (e.g. through public insurance, private insurance, out-of-pocket payment, etc.)".*[82] *"This is a recent decision which we are in the process of rolling out. The question will be directly* ***asked to the patient*** *by the investigator and this will be an inclusion criterion for the study. We discussed at length whether we would require actual documentation that post-trial access will be guaranteed (e.g. insurance contract, social security documents, etc.). This was seen as too complicated, given the variety of situations and countries in which we operate, and too much of a burden for patients."*[83]

Roche *write in their policy that their "preferred route is a written agreement obtained by* ***the national health system*** *assuring continuous medication and eligibility of all patients within national treatment systems, post completion of the Roche Sponsored Clinical Trial".*[84]

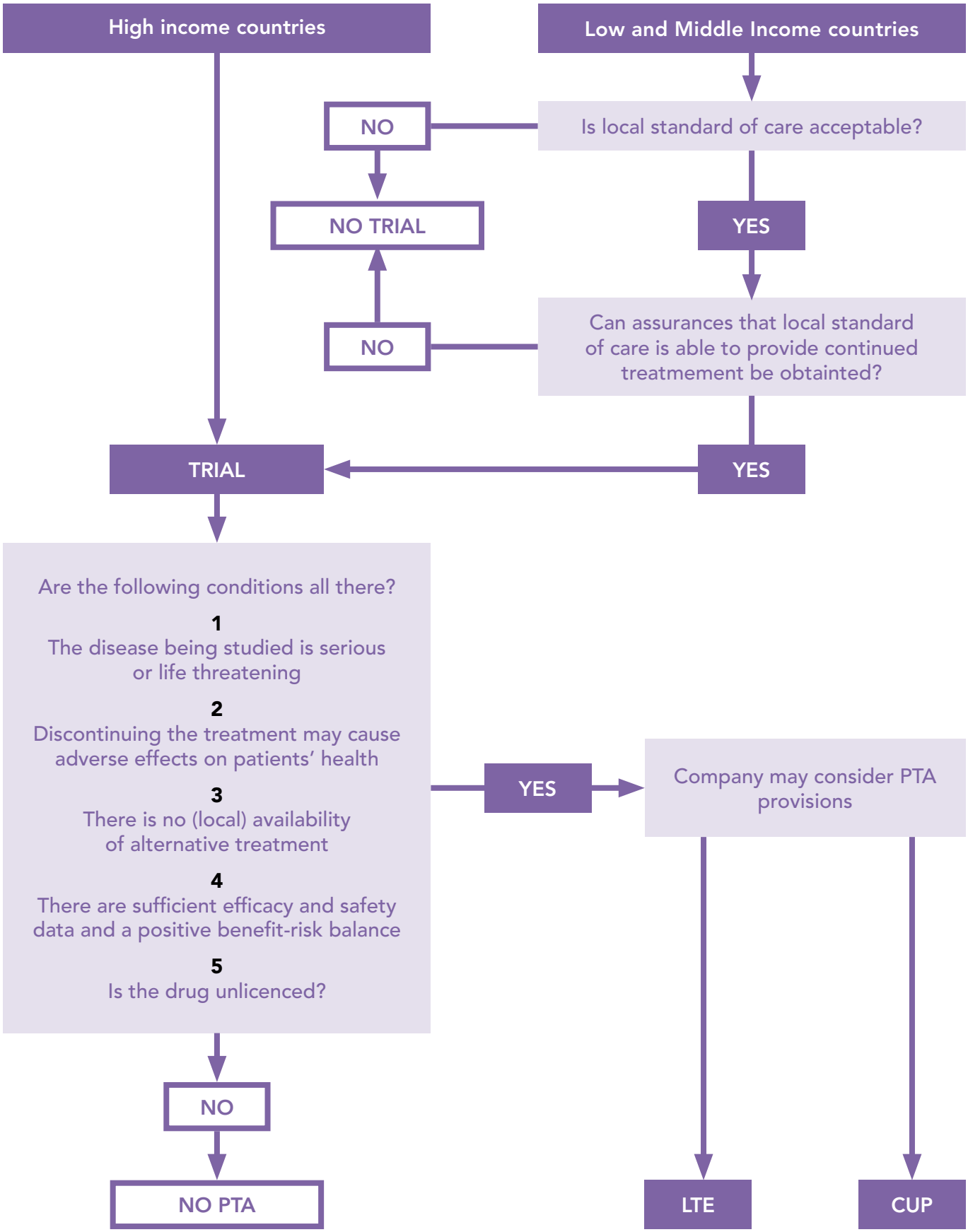
How the "guarantees" are obtained by the companies differ (through the investigator, the patient or the national health system). However, they all ensure beforehand that it is the national health system that will be responsible for PTA in low and middle income countries.

Examples of good PTA practice, as provided by the companies

The pharmaceutical industry is often widely criticised by campaigning organisations, but with this research our intention was simply to examine the industry's best practice in terms of PTA. We therefore expected pharmaceutical companies to welcome the opportunity to contribute with examples of their best practices. Surprisingly, this proved to be very challenging and time consuming. Companies were difficult to access, and examples of good PTA practices were scarce.

Among the companies that participated in this research, only five were able to provide cases of PTA. We collected a total of thirteen cases. Gilead offered a large number of examples, but only one is an example of PTA exclusively financed by the company. Sanofi offered six cases (four Long-Term Extension studies and two compassionate use programmes), only the latter are presented in the table below but all were good examples. GlaxoSmithKline provided SOMO with two cases, however one falls outside our scope. The one excluded is a case of Post-Approval Commitment study, requested by the European Medicines Agency prior to final authorisation of the drug, and therefore cannot be counted as PTA. Novartis mentioned a number of roll-over protocols[85] and provided two examples, of which one is presented below. The excluded one is an Expanded Access Program for those who are not eligible to participate in clinical trials and falls also outside our scope.

PTA decision tree based on SOMO's analyses of company policies



Long-Term Extension Studies

ClinicalTrials.gov identifier: NCT00158821[86]

- **Company:** Gilead Sciences
- **Drug brand name:** Viread®
- **Generic name:** tenovofir disoproxil fumarate (TDF)
- **Disease:** HIV
- **Countries:** United States, Brazil, Argentina, Dominican Republic
- **Enrolled:** 180
- **Date:** Start date March 2000, primary completion date December 2011

Related to the provision of PTA, Gilead indicate that: *"One of the issues is that you can only administer an investigational drug under protocol, so if you do a study and you finish the study, for those patients to access the drug, you can't just provide it. It has to be administered under a protocol. Authorities usually do not give special authorization; it's a highly regulated industry. It requires creating an open label protocol and collecting data and publishing the results."*[87]

As an example of such situations, Gilead offered the case of Viread®. In 2000, Gilead started a randomised double blind clinical trial to demonstrate the greater efficacy and safety of Viread®, lamivudine and efavirenz, in comparison with a regimen of stavudine, lamivudine and efavirenz. The drug was tested on antiretroviral naïve HIV-1 infected patients in a study that was solely sponsored by Gilead. According to the company,

PTA was provided to patients in the Dominican Republic and South America (Brazil and Argentina) for up to roughly ten years post completion of the study financed by Gilead. *"Since Viread® and Truvada®* [88] *were not yet approved in these countries when the original 3 year blinded study was completed, these drugs were provided through an expanded protocol until the drug was marketed, as required by the laws of those countries."*

The study protocol submitted by Gilead to the clinicaltrials.gov database documents what the company stated in their interview and confirms that, after the original 144 weeks, the trial was extended as an open label study multiple times for a total of 480 weeks (about ten years). In the first 246 weeks of extension, Gilead provided tenofovir DF in combination with lamivudine and efavirenz. In the last 144 weeks, only tenofovir DF was provided.

Long-Term Extension Studies

ClinicalTrials.gov Identifier: NCT01544179[89]

- **Company:** AstraZeneca
- **Drug:** Iressa®[90]
- **Generic name:** gefitinib
- **Disease:** (non small cell) lung cancer
- **Countries:** China, France, Germany, Hong Kong, Hungary, Italy, Japan, Korea, Russia, Spain, Taiwan
- **Enrolled:** 287
- **Date:** Started March 2012, estimated study completion date January 2016

Iressa® is a drug that is used to treat adults with non small cell lung cancer and has been granted marketing authorisation by the EMA on 24 June 2009. AstraZeneca provided a quote from an Iressa® study that is being conducted in China (and other sites) to illustrate how PTA is included in clinical trial protocols, although the protocol published in the clinicaltrial.gov database does not enclose the relevant quote. In their interview with SOMO, AstraZeneca stated that in every clinical trial and in every country where a trial is carried out, there will be a similar quote to the following: *"After the study analysis for PES and OS, patients will have their treatment unblinded. Patients receiving gefinitib and still considered to be gaining benefit will be provided an option for continued gefitinib treatment. This will be via the standard commercial and reimbursement routes or via open label study supply if the commercial supply route is not possible."*[91]

ClinicalTrials.gov identifier: NCT00712933[92]

- **Company:** GlaxoSmithKline
- **Drug brand name:** Benlysta®
- **Generic name:** belimumab
- **Disease:** systemic lupus erythematosus
- **Countries:** United Kingdom, Slovakia, Germany, United States, Austria, Korea, Colombia, Chile, Spain, Netherlands, Taiwan, Italy, Poland, Philippines, Argentina, Hong Kong, India, Brazil, Canada, Romania, Mexico, Israel, Russia, Sweden, Belgium, Peru, Czech Republic
- **Enrolled:** 733
- **Date:** Start date June 2008, estimated primary completion date March 2015

Benlysta® has been approved in Argentina since April 2012, but the extension study is still ongoing with the aim of ensuring participants with access to the drug. At the time of the interview, GlaxoSmithKline said: *"The current study was originally intended to run until approval from the local regulatory authorities. We are still trying to manage that and while that is going on, we haven't stopped the extension study yet. We have kept it going significantly longer than planned because of patient access issues. We are currently looking to close the study and we are considering other options to ensure that the patients without reimbursement to the drug are managed well. Until things become clear, we continue with the extension studies. In these studies, the drug is supplied through the continuation protocol with no charge to the patient"*. Patients are now transitioning off the study and are in the process of seeking reimbursement through local standard of care.[93]

Long-Term Extension Studies

ClinicalTrials.gov identifier: NCT01742299[94]

- **Company:** Novartis
- **Drug brand name:** Glivec®
- **Generic Name:** imatinib
- **Disease:** cancer
- **Countries:** United States, Switzerland, Turkey, United Kingdom, Thailand, China, Finland, France, Germany, Hong Kong, Romania, Singapore
- **Enrolled:** 149 (30 from China)
- **Date:** March 2013 – on going

Novartis conducts roll-over protocols. These protocols allow patients to continue treatment and have access to drug after the parent (and extension trials) end. Novartis states that they have ongoing roll-over protocols with drugs such as Tasigna, Afinitor, Glivec, Panobinostat and Signifor, and others. These roll-over protocols are compound-specific and are open to patients that have participated in a clinical trial with that compound, but that clinical trial has ended. One example of such a program is the Glivec (imatinib) roll–over protocol. Other countries that participate in this ongoing roll-over protocols, and that are not listed in the clinicaltrials.gov database, include Korea, India, Mexico, Peru and Argentina, as well as many other countries.

Named Patient Compassionate Use Programme

- **Company:** Sanofi
- **Drug:** Zaltrap®[95]
- **Generic name:** aflibercet
- **Disease:** colorectal cancer
- **Countries:** Australia, Austria, Belgium, Brazil, Canada, Cyprus, Greece, Hong Kong, India, Indonesia, Italy, Lebanon, Luxembourg, Malaysia, Mexico, Netherlands, Pakistan, Russian Federation, Singapore, South Africa, Spain, Switzerland, Syrian Arab Republic, United Kingdom and Uruguay
- **Enrolled:** 659
- **Date:** 22 March 2012 until present (still ongoing at the time of writing)

Zaltrap® is used in combination with FOLFIRI, a treatment combining irinotecan, 5-fuorouaracil and folic acid to treat adults with metastatic colorectal cancer. The drug has been approved in the European Union on 5 February 2013. Prior to the marketing authorisation, Sanofi made a Named Patient Compassionate Use Programme available in countries where the company submitted or intends to submit for registration and until marketing authorisation. Zaltrap® was available in combination with FOLFIRI-based chemotherapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen. According to Sanofi, the recruitment for this programme is no longer on-going, but the patients are still under treatment and follow up.

Cohorted Compassionate Use Programme

ClinicalTrials.gov Identifier: NCT01254279[96]

- **Company:** Sanofi
- **Drug:** Jevtana® [97]
- **Generic name:** cabazitaxel
- **Disease:** prostate cancer
- **Countries:** Argentina, Australia, Austria, Belgium, Bosnia, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Finland, Hungary, India, Ireland, Italy, Kazakhstan, Luxembourg, Malaysia, Mexico, Netherlands, Philippines, Poland, Portugal, Romania, Serbia, Singapore, Slovakia, Sweden, Taiwan and United Kingdom
- **Enrolled:** 984
- **Date:** Started 17 December 2010, estimated completion date December 2014

Sanofi implemented an Expanded Access Programme study to provide early access to cabazitaxel in patients with metastatic hormone refractory prostate cancer previously treated with a docetaxel-containing regimen. As it is stated in the protocol submitted to the database clinicaltrial.gov, the primary outcome measure of this early access programme was to provide early access to cabazitaxel in patients with metastatic hormone refractory prostate cancer.

The secondary outcome is to document the safety of cabazitaxel in those patients.

In the study protocol, it is clearly stated that, in each country, patient recruitment ends when cabazitaxel becomes commercially available, but considering the timing or delay in getting approval and reimbursement in the participating countries, cabazitaxel was therefore administered through this early access programme.

Conclusions

The current corporate practice

All the companies included in this research refer in their company policies to the Declaration of Helsinki, which includes the right to Post-Trial Access to Treatment (PTA).

At the same time, the companies are very clear that PTA will only be provided in very specific circumstances on a case-by-case basis. The standard practice followed is that the provision of post-trial care for clinical trial participants continues under the applicable health-care system of the host country. Companies say in general that they only consider providing PTA in case of non-licensed medicines for which no alternative treatments are available. This minimises the commitment to provide PTA enormously, since clinical trials testing new experimental drugs for which no alternative treatments exist are extremely scarce. Together with the other mentioned conditions (the serious nature of the disease, the serious consequences of discontinuation and a positive benefit-risk balance), the analysis undertaken for this report reveals that the practice of providing PTA is the exception rather than the rule.

PTA is also highly exceptional in low- and middle-income countries, where the need is much greater. Pharmaceutical companies do not want to become responsible for what they consider to be the responsibilities of the national health-care system related to continuing treatment after clinical trials. This is the reason for some companies avoiding conducting trials altogether in countries where the standard of care is too low to fulfill this responsibility and/or they might exclude vulnerable people with limited access to health care from their trials.

An extra step that companies take in LMICs is to obtain an assurance that the national health-care system will be able to provide continued treatment. This assurance may be obtained in different ways; from a written agreement with the national health system to a confirmation given by individual patients that they will have access to continuing treatment. (And therefore no PTA needs to be provided by the company.)

The reliance on such assurances might be deceptive. In fact, populations in LMICs are considered to be particularly vulnerable on the basis of lack of access to quality health care due to economic factors (e.g. low personal income of the patients and/or no reimbursement possibilities). Reliance on the national health-care system can, in fact, result in the cessation of the care available during the trial. In LMICs, there is a greater appeal for the company to take responsibility for providing PTA. The focus of the companies on obtaining these assurances, however, seems to shy away from these responsibilities and instead push the problem off to the host countries and the patients themselves.

What about 'best practice'?

The difficulty SOMO experienced in collecting good PTA examples from the companies in question and the absence of examples in the academic literature confirms the highly exceptional nature of PTA. The scarcity of access to treatment after a trial in LMICs is especially concerning.

In those exceptional circumstances where a company decides to arrange post-trial access to an unlicensed drug, it is done through an Open Label Extension Study or a Compassionate Use Programme. Open Label Extension Studies are the most common way to provide PTA in LMICs. However, ethical concerns voiced by academics, and to a certain extent also recognised by the companies, relate to the ambiguity between care and research in these studies. It is unclear whether such studies are done out of compassion or in order to gain long-term safety data for marketing reasons.

A contribution to a realistic high-level standard of PTA

Elements for a high-level standard of PTA are found in international ethical guidelines, relevant academic literature and in company policies. A common element relates to *advanced planning*. Before the trial starts arrangements must be clear and negotiated when necessary. Moreover, it can be found in the guidelines, literature and policies that those arrangements must be specified in the clinical trial protocol and disclosed to trial participants during the informed consent process.

The need for a clear *allocation of responsibilities* (including financial responsibilities) in the planning phase of a clinical trial and a broader definition of PTA is only supported by the international guidelines and the academic literature.

Both in the case of licensed or unlicensed drugs, PTA should not be limited to the provision of the investigational drug, but should leave the possibility open to *include other appropriate care and benefits* such as other effective interventions. This definition makes it possible to extend the PTA to larger populations than the trial participants only. This broader definition can also be more practical for companies. More routes for PTA open up so the companies do not always have to turn to Open Label Extension Studies to provide unlicensed drugs.

Another strong point to mention, supported by the guidelines, is that *the lack of PTA arrangements needs to be justified* to research ethics committees.

Recommendations

SOMO considers the following recommendations relevant to contribute towards better PTA practice in future.

- The ICH should consider including a section on PTA arrangements in their guidance documents, such as in the E3 guidelines for the clinical study reports and E6 guidelines for good clinical practice. As the ICH guidelines are incorporated in EU legislation, this would be binding in nature.

- The World Medical Association should consider re-adopting the language applied in the 2008 version of the Declaration of Helsinki and include again the wording "other appropriate care or benefits" as provisions of PTA.

- The World Health Organization (WHO) should consider including a field for PTA in the 'WHO Data Set' to increase transparency on PTA arrangements.

- (EU) Regulatory Authorities should ensure that the applicant for a marketing authorisation provides a description of the situation of trial participants with regard to PTA. Also, the applicant should describe the provisions made for post-trial access to treatment and medical care for study participants depending on their localization and the treatment and medical care otherwise available. This information can form part of the clinical study report section on ethical considerations in accordance with ICH E3.

- (EU) Regulatory Authorities should identify those studies that may give rise to special ethical concerns regarding access to post-trial treatment and, where applicable, to seek additional assurance that the solution was appropriate and ethically acceptable.

- (EU) Regulatory Authorities should summarise this information in public assessment reports.[98]

- Pharmaceutical companies should act with 'due diligence' in relation to the issue of PTA in line with the UN Guiding Principles on Business and Human Rights.

In more practical terms, this would require that pharmaceutical companies acting as sponsors of clinical trials should:

- Have an adequate policy commitment on PTA; a commitment only to provide PTA in cases of non-licensed medicines for which no alternative treatment exists is too limited for LMICs. Alternative treatments or other appropriate care and benefits should also be considered when addressing the issue of PTA.

- Act with 'due diligence', involving:
  - Identifying and assessing the negative impacts of conducting clinical trial in LMICs, including access to treatment and appropriate care during and after the trial. Including trials that are conducted by third parties on behalf of the company.
  - Taking action to prevent and mitigate the impacts identified.
  - Tracking the performance and evaluating how effectively the impacts are being addressed.
  - Communicating externally in order to account for how the impacts are addressed.

- Have an effective grievance mechanism in place for participants who may be negatively impacted, so that grievances can be addressed early and remediated directly.

End notes

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Colophon

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