



Availability of post-trial access in clinical trials: a review of clinical trial protocols submitted to the Research Ethics Board of the University of the Philippines Manila

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3 **1 Availability of post-trial access in clinical trials: a review of clinical trial protocols submitted to**
4 **2 the Research Ethics Board of the University of the Philippines Manila**

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12 **6 Abstract**
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14 7 Ethics guidelines such as the Declaration of Helsinki and the CIOMS International Ethical
15 8 Guidelines for Health-related Research Involving Humans require the sponsors, in cooperation
16 9 with relevant stakeholders, to provide post-trial access (PTA) to intervention and knowledge,
17 10 especially in clinical trials held in resource-poor regions. To date, we have very limited
18 11 knowledge in terms of whether PTA is provided at all, and in what form. To partially address
19 12 this current limitation, this study wished to explore whether, for which type of drugs, and in
20 13 what form PTA is provided in the Philippines.

21 14 We looked at all the clinical trial protocols submitted to the University of the Philippines Manila
22 15 from 2012 to 2017. A total of 193 clinical trial protocols were included in the study. To identify
23 16 whether, for which drug type, and in what form PTA is provided, we gathered the following
24 17 information: start and end date of the trial, name of study drug, tested indication of the study
25 18 drug, region the sponsor is from, type/category of the study drug, type of funding agency,
26 19 provisions for PTA (yes or no), and the explanation for the provisions. PTA provisions were
27 20 further described to determine what form PTA was provided and which types of drug were
28 21 given PTA.

29 22 Of the 193 protocols, 51.81% indicated PTA, the most common form being the provision or
30 23 sharing of information (40 protocols). None of the protocols provided PTA in the form of access
31 24 to intervention after the trials, with the possible exemption of 10 protocols that declared future
32 25 evaluation of the sponsor for PTA depending on patient need, and another seven that might
33 26 offer the option to transfer to an open-label extension study after the trial. More work is
34 27 needed if PTA, as stipulated in ethics guidelines, is to be reflected in reality.
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46 29 **Keywords:** post-trial obligations, post-trial access, research ethics, clinical trials
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30 Introduction

31 Clinical trials are moving quickly from high income to low and middle income countries (LMICs)
32 [1–3]. In the EU, the number of clinical trials submitted to the European Medicines Agency
33 (EMA) for marketing authorization applications from the rest of the world region (ROW) tripled
34 from 2005 to 2011 [4], and has overtaken the number of such clinical trials from the EU and
35 North America since 2011 [4].

36 The globalization of clinical trials may be explained by several factors, the most prominent of
37 which are cost savings [2]; shorter recruitment timelines [2,5]; and less stringent regulatory
38 constraints [2,5]. That clinical trials are conducted for these reasons is not necessarily ethically
39 problematic if, aside from the usual ethics requirements of informed consent and ethics
40 committee review, these trials contribute to increased access to essential and innovative
41 medicines in the region. The conduct of clinical trials can have a role in increasing access to
42 medicines if, specifically, and in terms of ethics guidelines, post-trial access (PTA) is in place. The
43 Declaration of Helsinki Article 20, for example, states the following:

44 Medical research with a vulnerable group is only justified if the research is responsive to
45 the health needs or priorities of this group and the research cannot be carried out in a
46 non-vulnerable group. In addition, this group should stand to benefit from the knowledge,
47 practices or interventions that result from the research [6].

48 The CIOMS *International Ethical Guidelines for Health-related Research Involving Humans*
49 provides more guidance on “research conducted in resource-poor settings”:

50 As part of their obligation, sponsors, and researchers must also: make every effort, in
51 cooperation with government and other relevant stakeholders, to make available as
52 soon as possible any intervention or product developed, and knowledge generated, for
53 the population or community in which the research is carried out, and to assist in
54 building local research capacity [7].

55 While PTA is stipulated in the guidelines, it is another concern whether such stipulation is in
56 fact in effect. The provision of post-trial access to research participants is mandated by law in
57 various degrees in a few countries, such as in Argentina, Brazil, Chile, Finland, and Peru [8].
58 Through a study of corporate best practices based on corporate responses to a survey, we also
59 know that the provision of PTA, even in LMICs, is sponsor-defined, i.e., sponsors are at liberty to
60 provide PTA or not [9]; that it is mostly provided in “exceptional circumstances” (i.e., the
61 situation is life-threatening; discontinuing treatment would result to adverse effect on health of
62 the participant; no local alternative treatment; and a positive benefit-risk balance of the safety-
63 efficacy of the treatment) [9]; and that PTA is narrowly defined to refer to the provision of yet
64 non-licensed drugs to patient-participants [9]. However, though previous studies point to the
65 weaknesses of the implementation of PTA, we still do not know the rate that PTA is provided, if
66 at all, whether in exceptional circumstances or not. The only study we know that looked at the

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3 67 rate of PTA was a nonprobability qualitative study of 34 protocols submitted to the Mexican
4 68 Sub-Commission for Ethics in Research in 2004, the results of which showed that PTA was not
5 69 considered in any of the cases [10]. Though this research points to a specific direction, i.e., that
6 70 PTA is not provided, we cannot know for sure that PTA was in fact not present, considering that
7 71 this was a qualitative study. Since saturation point was used to choose the 34 protocols and not
8 72 the entire population or at least a statistical sampling, we could not, with certainty, state that
9 73 there indeed were no PTA provisions in the other protocols submitted within the said year.
10 74 Also, we expected to see some trend. Lastly, we would also probably wish to look at PTA
11 75 provisions in more than one LMIC. To add to the body of knowledge on the rate of PTA, *our*
12 76 *study intended to explore whether, for which type of drugs, and in what form PTA is provided in*
13 77 *the Philippines.*

18 78 **Methodology**

19 79 Our study aimed to, at least, partially address the limitations in the literature by looking at all
20 80 the international clinical trial protocols submitted to the University of the Philippines Manila
21 81 Research Ethics Board (UPMREB) from 2012 to 2017. These years would sufficiently document
22 82 changes in PTA provision trend, if any, from the year of the latest version of the Declaration of
23 83 Helsinki (2013) and the 2016 version of the CIOMS Ethics Guidelines. UPMREB data on PTA
24 84 provisions is interesting for at least three reasons: 1) the Philippines is top three contributor in
25 85 Asia in terms of the number of patients in pivotal clinical trials submitted to the EMA for
26 86 marketing authorization application [4]; 2) UP Manila has a good cross section of multi-center
27 87 pharmaceutical trials conducted in the Philippines; and lastly, 3) according to a January 2018
28 88 TrialTrove search, UP Manila has the most number of clinical trial investigators nationally, and
29 89 second in the country in terms of the number of international clinical trials. In the Philippines,
30 90 the major research ethics committees are all recognized by the Forum for Ethical Review
31 91 Committees in the Asian and Western Pacific Region and accredited by the Philippine Health
32 92 Research Ethics Board; hence, the procedures, standards, and requirements of the major
33 93 research ethics committees are comparable.

34 94 The study was submitted to the UPMREB for review and was granted exemption from ethical
35 95 review. A total of 193 clinical trial protocols were included in the study. PTA information is
36 96 explicitly required in protocol submission to the UPMREB. The protocol template requires the
37 97 investigator to indicate whether or not the protocol has PTA provision stated in the informed
38 98 consent document, with an option to indicate that PTA is not applicable. To identify whether,
39 99 for which drug type, and in what form PTA is provided, we gathered the following information
40 100 from these protocols: start and end date of the trial, name of study drug, tested indication of
41 101 the study drug, region the sponsor is from, type/category of the study drug, type of funding
42 102 agency, provisions for PTA (yes or no), and the explanation for the provisions. From the Excel
43 103 file, we then made a count of the number of protocols submitted to UPMREB per year,

104 categorized the study drugs based on indication and the US new drug application (NDA)
105 classification^c.

106 We counted the 'yes' responses on the question *whether the trial provides PTA*. We then
107 collated their statements on PTA provision and categorized them to identify *in what form* PTA
108 was provided. Lastly, to identify *for which types of drugs* PTA was provided, we grouped PTA
109 provisions based on drug types based on indication and NDA classification.

110 Results

111 Number of trials and types of study drugs

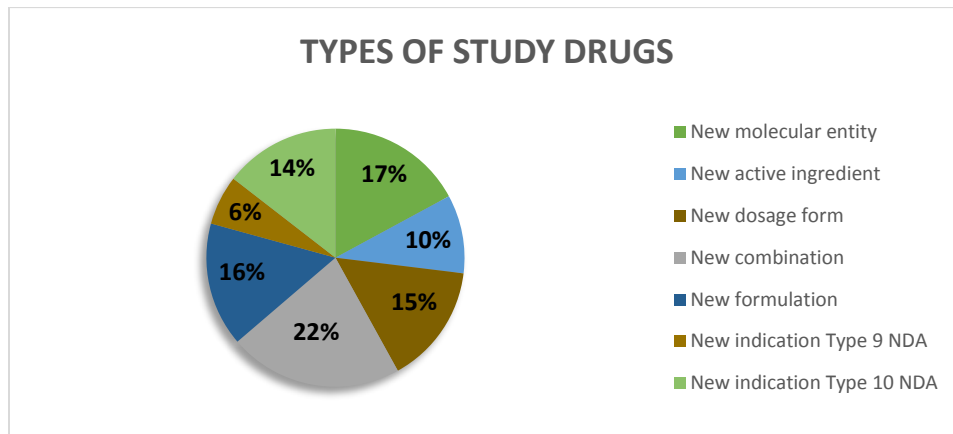
112 The clinical trials were categorized based on the condition/disease that the clinical trial is
113 studying. Most of the study drugs were meant to address non-communicable diseases
114 (76.17%), most of which were for respiratory, neoplastic, and cardiovascular diseases (see Table
115 1 below).

List of Diseases	Number of Clinical Trials
NON-COMMUNICABLE DISEASES	
Respiratory	30
Neoplasms	21
Cardiovascular	18
Mental/neurological	17
Autoimmune Diseases	16
Diabetes and Kidney	15
Pain	8
Musculoskeletal Disorder	6
Skin disease	5
Sense organ	3
Digestive diseases	2
Genetic disease	2
Others	2
Urinary disease	1
Anemia	1
TOTAL	147 (76.17%)
COMMUNICABLE DISEASES	
Bacterial/viral (vaccine)	29
Other bacterial	11
Other viral	2
Fungal infection	1
Respiratory tract infection	3
TOTAL	46 (23.83%)

^c The classification is as follows: Type 1: new molecular entity; Type 2; new active ingredient; Type 3: new dosage form; Type 4: new combination; Type 5: new formulation or other differences (e.g., new indication, new applicant, new manufacturer); Type 6: new indication or claim, same applicant; Type 7: previously marketed but within an approved NDA; Type 8: Rx to over-the-counter; Type 9: new indication or claim, not to be marketed under Type 9 NDA after approval; Type 10: new indication or claim, drug to be marketed under Type 10 NDA after approval[11].

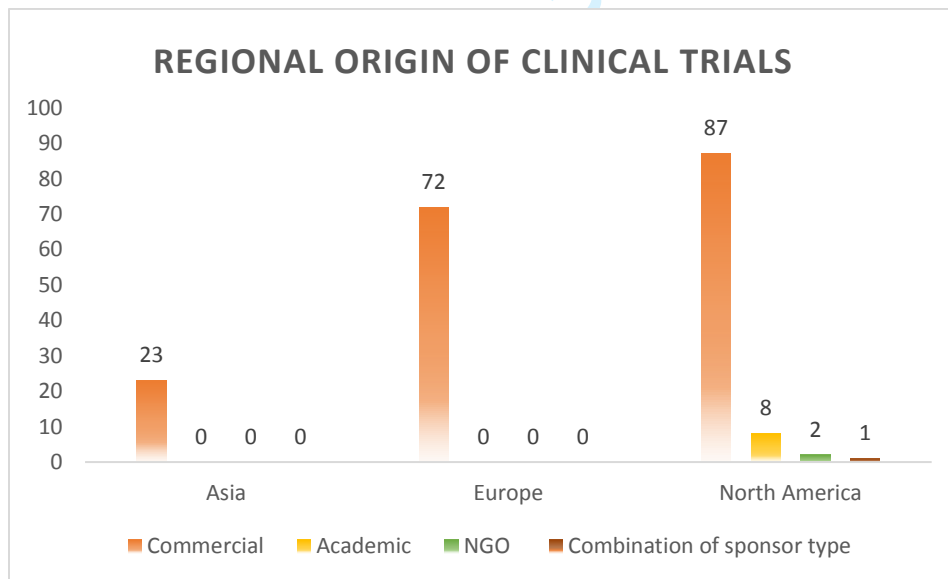
116 *Table 1: Condition/disease addressed by clinical trials in UPM, 2012-2017*

117 In terms of types of study drugs, most of the study drugs were new combinations, new
 118 molecular entities, and new formulations (see Figure 1).



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 120 *Figure 1: Types of study drugs in clinical trials in UPM, 2012-2017*

121 The clinical trials were predominantly sponsor-initiated studies from pharmaceutical companies
 122 in North America, Europe, and Asia (in descending order in terms of number of trials; see Figure
 123 2). Note that no local trials were documented.

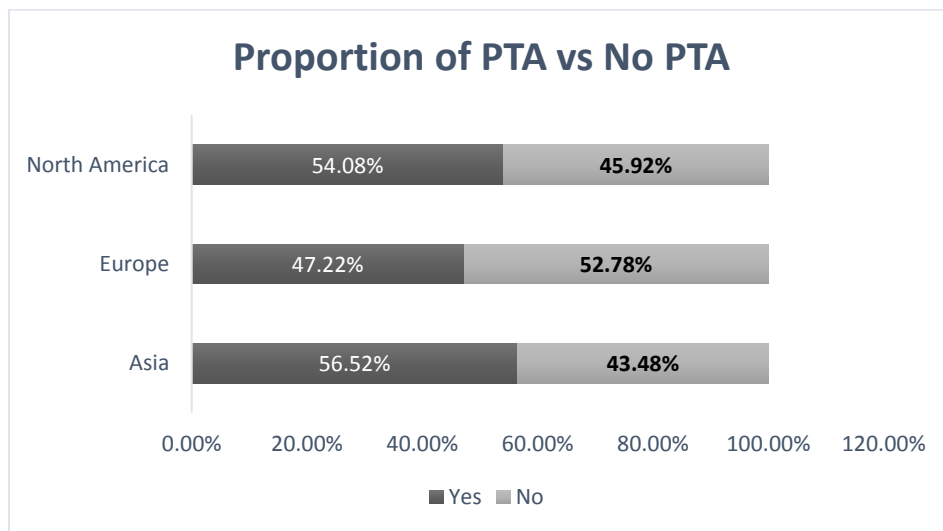


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 125 *Figure 2: Sponsor origin of clinical trials in UPM, 2012-2017*

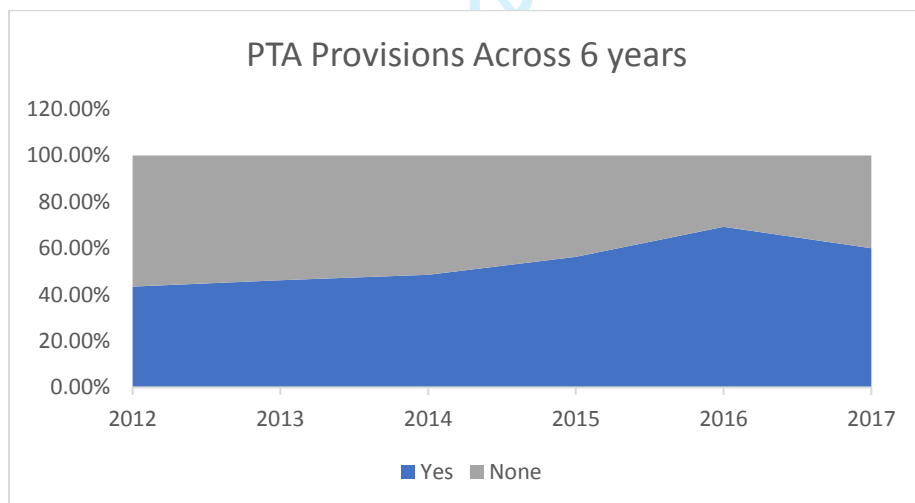
126 **Post-trial Access Provisions**

127 Among the 193 protocols reviewed from 2012 to 2017, 100 (51.81%) protocols indicated some
 128 form of post-trial provision, while 93 (48.19%) indicated that PTA is not applicable. The
 129 proportion of protocols with and without the indication of post-trial provisions remains
 130 approximately similar across the different clinical trial regional origins (Figure 3). This trend is

131 relatively consistent throughout the years (Figure 4), in spite of the declining trend in clinical
 132 trial submissions.

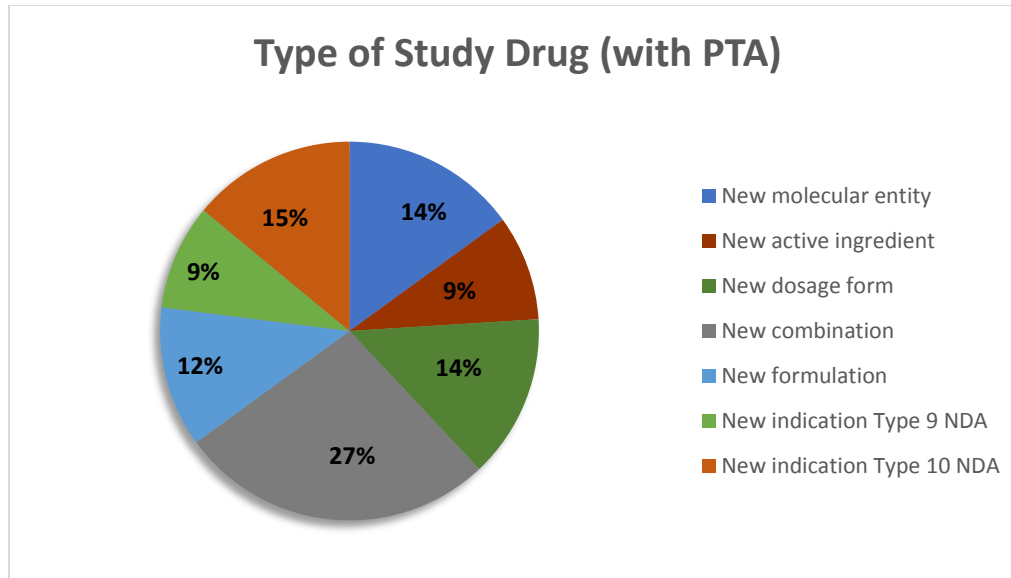


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 134 *Figure 3: Proportion of clinical trials that indicated PTA versus those without a PTA indication*



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 136 *Figure 4: Proportion of clinical trials that indicated PTA versus those without a PTA indication,*
 137 *2012-2017*

138 When these 100 protocols with indications of PTA were grouped according to type of study
 139 drug (Figure 5), the trend is comparatively similar to the total number of clinical trials grouped
 140 according to study drug type in Figure 1, i.e., most of the PTA indications were in new
 141 combinations and new molecular entities.

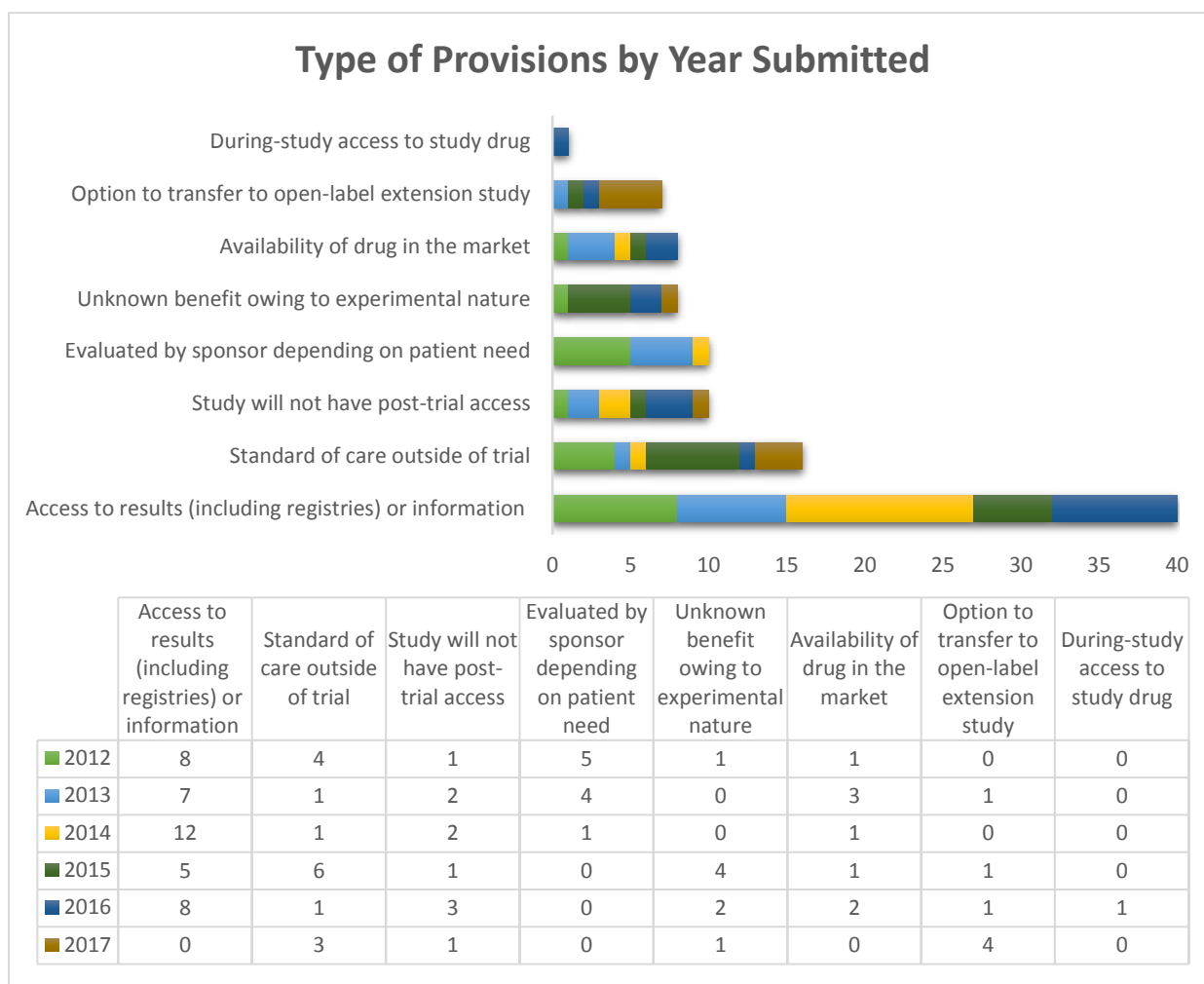


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143 *Figure 5: PTA according to type of study drug*

144 Among the protocols that indicated a post-trial provision, the PTA identified by the sponsors
 145 may be categorized as follows: (1) access to trial results (including registries) or information; (2)
 146 presence of standard of care outside the trial; (3) no PTA of the study drug will be provided; (4)
 147 PTA to be evaluated by sponsor depending on patient need; (5) unknown benefit owing to
 148 experimental nature of the study; (6) drug will be made/is available in the market; (7) option to
 149 transfer to open-label extension study; and (8) during-study access to study drug (Table 2).

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152 *Table 2: Type of provisions by year of clinical trials submitted to UP Manila*

153 In Table 2, the most commonly indicated PTA is access to results, including publication of
 154 results in a clinical trial registry or in medical journals, or the sharing of information, including
 155 safety information and other information that could potentially be useful in clinical decision-
 156 making. After access to information, the next commonly indicated PTA is the availability of
 157 standard of care outside of the trial as an alternative to trial participation. In practice, the IRB
 158 actively seeks the PTA provision only when the disease is rare or incurable or treatment is very
 159 expensive, and only when the results are effective and safe.

160 **Discussion**

161 The results of this study must be viewed in terms of the requirements of ethics guidelines,
 162 specifically of the Declaration of Helsinki and CIOMS, as quoted above. Helsinki requires the
 163 sharing of knowledge, practices, or interventions; however, this declaration is silent on when
 164 PTA is relevant to which type of study. CIOMS provides more clarity in this matter, specifically,
 165 that PTA is (1) the responsibility of the sponsor in cooperation with the government and other

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3 166 relevant stakeholders; and (2) this responsibility consists in making the product developed *and*
4 167 knowledge generated to be available as soon as possible to the population or community
5 168 where the research was carried out.

7
8 169 The Declaration of Helsinki provision on post-trial access describes post-trial obligations as
9 170 providing access to appropriate care or to relevant information after research [6]. In the
10 171 literature, access to **appropriate care** has been interpreted to mean affordable access or
11 172 “reasonable availability of beneficial pharmaceuticals or medical treatments” [12]; continued
12 173 access to study interventions that have demonstrated significant benefit and for transitioning
13 174 participants who continue to need care and preventive measures after the research to
14 175 appropriate health services [13]; or an obligation to facilitate sustainable access or subsidized
15 176 access to new interventions in host communities [14].

17 177 In our study, several of the types of declared PTA by the sponsors showed that some sponsors
18 178 either have their own definition of PTA that is different from what ethics guidelines provide,
19 179 different from what the literature refers to as appropriate care, or that the sponsors have no
20 180 idea what ethics guidelines or the literature say about PTA. The following PTA categories are
21 181 either not in agreement with the ethical definition of PTA or are directly opposed to it: (1)
22 182 presence of standard of care outside the trial; (2) no PTA of the study drug will be provided; (3)
23 183 unknown benefit owing to experimental nature of the study; (4) drug will be made or is
24 184 available in the market; and (5) during-study access to study drug.

25 185 The literature suggests that the practice of providing PTA differs across countries and contexts.
26 186 The example of Brazil and Argentina, for example, refer to PTA as access to the interventional
27 187 drug of the patient participants after the trial and so long as they need it and before access to
28 188 other means becomes available [8]. This type of PTA was not directly observed in our study,
29 189 though the 5% (i.e., 10 of the 193) of the studies where PTA will be evaluated by the sponsor
30 190 based on patient-participants’ needs *could* lead to this sort of access. At the same time, PTA
31 191 may also mean the transition of the patient-participants into extension studies sponsored by
32 192 pharmaceutical manufacturers until the intervention becomes available in the health system
33 193 [13, 15, 16], though admittedly this is not always possible [17]. This was the case for 4% (i.e., 7
34 194 of the 193) of the clinical trials in our study. Lastly, the provision of PTA may also mean
35 195 incorporating in the trial design the continued access to a proven beneficial intervention (e.g.
36 196 WHO recommendations that PTA, in terms of availability of the vaccine to the community, be a
37 197 requirement before conducting a clinical trial on a respiratory syncytial virus vaccine in LMICs)
38 198 [18]. This type of PTA was not observed in our study.

39 199 The number of protocols that indicated PTA (51.81%) among the clinical trials reviewed seemed
40 200 encouraging, at first. However, when we considered the types of PTA declared by the sponsors,
41 201 we realized that the most that the population or community might get is information that may
42 202 be clinically relevant in the future (40 protocols). In addition, there were seven protocols which
43 203 might offer patient-participants the option to transfer to an open-label extension study, plus
44 204 the 10 where PTA will be evaluated by the sponsor post-trial. In practice, sponsors provide

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3 205 post-trial access through follow-up studies to see long term effects on patients, open label
4 206 extension studies, expanded access, and compassionate use, among others [9]. At best, these
5 207 drugs are made available on a case to case basis [9] and not as a standard requirement to
6 208 comply with the Declaration of Helsinki and CIOMS.

9 209 Out of the 100 protocols with post-trial provisions, there were 10 where the sponsor declared
10 210 the future evaluation of PTA depending on patient need. This means that in all instances, *none*
11 211 of the sponsors made PTA arrangements before the beginning of the study. Recall that CIOMS
12 212 stipulates that before undertaking research in a community or population with limited
13 213 resources, sponsors and investigators must “make every effort to ensure that any intervention
14 214 or product developed, or knowledge generated, will be made reasonably available for the
15 215 benefit of that population or community.” From the perspective of CIOMS, only the 40
16 216 protocols that declared information sharing as PTA *partially* complied with the PTA imperative,
17 217 and depending on how the sponsor decides on the situation, maybe the 17 others, too, who
18 218 might consider PTA after sponsor evaluation or provide PTA in the form of an open-label follow
19 219 up study. All others did not comply with PTA requirements at all.

22 220 According to another study, pharmaceutical companies mostly provide PTA in “exceptional
23 221 circumstances” (i.e., the situation is life-threatening; discontinuing treatment would result to
24 222 adverse effect on health of the participant; no local alternative treatment; and a positive
25 223 benefit-risk balance of the safety-efficacy of the treatment) [9]. Even when we narrowly define
26 224 PTA this way, apparently none of the protocols saw the situation as exceptional enough to
27 225 consider PTA pre-trial, and only 10 declared possible PTA subject to sponsor evaluation. This is a
28 226 cause for concern because, first, at least some of the study drugs were meant to address
29 227 diseases that could be life threatening such as the various kinds of neoplastic diseases or severe
30 228 respiratory, autoimmune, or cardiovascular diseases. Second, we also know that a big
31 229 proportion of the patient-participants of the trials in UPM were likely to discontinue with
32 230 treatment, especially for very costly drugs, for several poverty-related reasons: there is no
33 231 universal access to health care in the Philippines and health care is usually out of pocket;
34 232 poverty rate is currently at 21.6% [19]; and the Philippine General Hospital of the UPM, as a
35 233 public hospital, usually caters to patients who are unable to afford private hospitals.

36 234 Assuming that the study showed positive benefit/risk balance of efficacy-safety of the study
37 235 drug, all the corporate indicators of what is “exceptional” seemed present in at least some of
38 236 the studies. Since sponsors are usually aware of this situation, it must further be explored why
39 237 none of the protocols considered PTA arrangements pre-trial, on the condition that there is
40 238 positive benefit-risk balance of the safety-efficacy profile of the study drug, and only 10
41 239 indicated this probability subject to sponsor evaluation. Literature offers to explain
42 240 noncompliance to PTA. According to Wang and Ferraz, commitment to post-trial obligations
43 241 may be onerous and may impede future research, regardless of who will be sponsoring these
44 242 obligations, as it may redirect costs from funding other potential studies such as chronic and

243 rare diseases [20]. Whether this reason holds from an economic perspective remains to be
244 seen.

245 To date, none of the clinical trial protocols evaluated by UPMREB *fully* complied with ethical
246 requirements for PTA. Through no fault of the IRB, there remains a lack of standardized
247 governance to implement post-trial obligations [21]. If PTA is to be fully reflected in reality,
248 clearly more work has to be done in terms of clarification of what the term means (i.e., what
249 must be provided, in what manner, to what extent); ensuring common understanding of the
250 term among the various stakeholders; a PTA-encouraging environment; and a structure that
251 facilitates stakeholder cooperation for PTA.

252 **Conclusion**

253 More than half (100 out of 193) of the clinical trials submitted in UPMREB indicated post-trial
254 provisions and the most common post-trial access provision identified is access to information.
255 Post-trial access will be dependent upon the evaluation of the sponsor based on patient need
256 and the option to transfer to open-label extension study in ten (5%) and seven (4%) clinical
257 trials, respectively. It can be deduced that none of the sponsors made PTA arrangements pre-
258 trial, and at best, are made available on a case to case basis. This result is alarming since these
259 clinical trials involved life-threatening diseases, and especially for researches conducted in
260 LMICs where there is no adequate access to marketed drugs and even to universal health care,
261 patients may not be able to access these drugs after the trial ends. As such, post-trial access to
262 study drugs remains a challenge. There are existing guidelines stipulating post-trial obligations
263 but there is poor compliance among the pharmaceutical sponsors. Furthermore, despite the
264 CIOMS and Helsinki provisions on post-trial access, there seems to be no international
265 consensus around it. Based on its current status, achieving post-trial access, as stipulated in
266 ethics guidelines, would need further and considerable work.

267 **Declaration**

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269 *Framework Programme (FP7-PEOPLE-2013-COFUND) under grant agreement n° 609020 -*
270 *Scientia Fellows.*

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For Peer Review Only

1 **Availability of post-trial access in clinical trials: a review of clinical trial protocols submitted to**
 2 **the Research Ethics Board of the University of the Philippines Manila**

3 Edlyn B Jimenez^a, Jessa Mae P Virtudazo^a, Cristina E Torres^a, Rosemarie DLC Bernabe^b

6 **Abstract**

7 Ethics guidelines such as the Declaration of Helsinki and the CIOMS International Ethical
 8 Guidelines for Health-related Research Involving Humans require the sponsors, in cooperation
 9 with relevant stakeholders, to provide post-trial access (PTA) to intervention and knowledge,
 10 especially in clinical trials held in resource-poor regions. To date, we have very limited
 11 knowledge in terms of whether PTA is provided at all, and in what form. To partially address
 12 this current limitation, this study ~~wished~~wishes to explore whether, for which type of drugs, and
 13 in what form PTA is provided in the Philippines.

14 We looked at all the clinical trial protocols submitted to the University of the Philippines Manila
 15 from 2012 to 2017. A total of 193 clinical trial protocols were included in the study. To identify
 16 whether, for which drug type, and in what form PTA is provided, we gathered the following
 17 information: ~~start~~begin and end date of the trial, name of study drug, tested indication of the
 18 study drug, region the sponsor is from, type/category of the study drug, type of funding agency,
 19 provisions for PTA (yes or no), and the explanation for the provisions. PTA provisions were
 20 further described to determine what form PTA was provided and which types of drug were
 21 given ~~for~~ PTA.

22 Of the 193 protocols, 51.81% indicated PTA, the most common form being the provision ~~or~~
 23 ~~sharing~~ of information (40 protocols). None of the protocols provided PTA in the form of
 24 access to intervention after the trials, with the possible exemption of 10 protocols that declared
 25 future evaluation of the sponsor for PTA depending on patient need, and another seven that
 26 might offer the option to transfer to an open-label extension study after the trial. ~~More~~A lot of
 27 work ~~is needed~~ needs to be done if PTA, as stipulated in ethics guidelines, is to be ~~fully~~
 28 in reality.

30 Keywords: post-trial obligations, post-trial access, research ethics, clinical trials

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31 Introduction

32 Clinical trials are ~~moving~~ quickly ~~moving~~ from high income to low and middle income countries
 33 (LMICs) ~~[(1-3)]~~. In the EU, the number of clinical trials submitted to the European Medicines
 34 Agency (EMA) for marketing authorization applications from the rest of the world region (ROW)
 35 tripled from 2005 to 2011 ~~[(4)]~~, and ~~since 2011~~ has overtaken the number of such clinical trials
 36 from the EU and North America ~~since 2011~~ ~~[(4)]~~.

37 The globalization of clinical trials may be explained by several factors, the most prominent of
 38 which are cost savings ~~[(2)]~~; shorter recruitment timelines ~~[(2,5)]~~; and less stringent regulatory
 39 constraints ~~[(2,5)]~~. That clinical trials are conducted for these reasons is not necessarily ethically
 40 problematic if, aside from the usual ethics requirements of informed consent and ethics
 41 committee review, these trials contribute to increased access to essential and innovative
 42 medicines in the region. ~~The conduct of clinical trials can have a role in increasing access to~~
 43 ~~medicines if, specifically~~Specifically, and in terms of ethics guidelines, ~~that~~ post-trial access (PTA)
 44 is in place. The Declaration of Helsinki Article 20, for example, states the following:

45 Medical research with a vulnerable group is only justified if the research is responsive to
 46 the health needs or priorities of this group and the research cannot be carried out in a
 47 non-vulnerable group. In addition, this group should stand to benefit from the knowledge,
 48 practices or interventions that result from the research ~~[(6)]~~.

49 The CIOMS *International Ethical Guidelines for Health-related Research Involving Humans*
 50 provides ~~a bit~~ more guidance on “research conducted in resource-poor settings”:

51 As part of their obligation, sponsors, and researchers must also: make every effort, in
 52 cooperation with government and other relevant stakeholders, to make available as
 53 soon as possible any intervention or product developed, and knowledge generated, for
 54 the population or community in which the research is carried out, and to assist in
 55 building local research capacity ~~[(7)]~~.

56 ~~While PTA is stipulated in the guidelines, it is another concern whether such stipulation is in~~
 57 ~~fact in effect. The provision of post-trial access to research participants is mandated by law in~~
 58 ~~various degrees in a few countries, such as in Argentina, Brazil, Chile, Finland, and Peru [8].~~

59 ~~Now, it is one thing that PTA is stipulated in the guidelines and quite another on whether such~~
 60 ~~stipulation is in fact in effect. To date, we know only of one country with PTA legislation, i.e., Brazil[8].~~

61 Through a study of corporate best practices based on corporate responses to a survey, we also
 62 know that the provision of PTA, even in LMICs, is sponsor-defined, i.e., sponsors are ~~at~~ liberty
 63 to provide PTA or not ~~[9](8)]~~; that it is mostly provided in “exceptional circumstances” (i.e., the
 64 situation is life-threatening; discontinuing treatment would result to adverse effect on health of
 65 the participant; no local alternative treatment; and a positive benefit-risk balance of the safety-
 66 efficacy of the treatment) ~~[9](8)]~~; and that PTA is narrowly defined to refer to the provision of
 67 yet non-licensed drugs ~~to patient-participants~~ ~~[9](8)]~~. However, though ~~previous studies~~
 68 ~~point~~this study ~~points~~ to the weaknesses of the implementation of PTA, we still do not know the

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rate that PTA is provided, if at all, whether in exceptional circumstances or not. The only study we know that looked at the rate of PTA was a ~~nonprobability~~~~nonprobabilistic~~ qualitative study of 34 protocols submitted to the Mexican Sub-Commission for Ethics in Research in 2004, the results of which showed that PTA was not considered in any of the cases [10](9). Though this research points to a specific direction, i.e., that PTA is not provided, we cannot know for sure that PTA was in fact not present, considering that this was a qualitative study. ~~Since~~~~Because~~ a saturation point was used to choose the 34 protocols and not the entire population or at least a statistical sampling, we could not ~~with certainty~~, ~~state say~~, that there indeed were no PTA provisions in the other protocols submitted within the said year. Also, we ~~expected would probably wish~~ to see some trend. Lastly, ~~we~~ would also probably wish to look at PTA provisions in more than one LMIC. To add to the body of knowledge on the rate of PTA, *our study intended wishes to explore whether, for which type of drugs, and in what form PTA is provided in the Philippines.*

Methodology

Our study ~~aimed wishes~~ to, at least, partially address the limitations in the literature by looking at all the international clinical trial protocols submitted to the ~~Research Ethics Board of the~~ ~~University of the Philippines Manila~~ ~~Research Ethics Board (UPMREB)~~ ~~(UPM-REB)~~ from 2012 to 2017. These years would sufficiently document changes in PTA provision trend, if any, from the year of the latest version of the Declaration of Helsinki (2013) and the 2016 version of the CIOMS Ethics Guidelines. UPMREB data on PTA provisions is interesting for at least three reasons: ~~1)~~ the Philippines is top three contributor in Asia in terms of the number of patients in pivotal clinical trials submitted to the EMA for marketing authorization application [(4); ~~2)~~ UP Manila has a good cross-section of multi-center pharmaceutical trials conducted in the Philippines; and lastly, ~~3)~~ according to a January 2018 TrialTrove search, UP Manila has the most number of clinical trial investigators nationally, and second in the country in terms of the number of international clinical trials. In the Philippines, the major research ethics committees are all ~~recognized~~~~accredited~~ by the Forum for Ethical Review Committees in the Asian and Western Pacific Region, and ~~accredited by the Philippine Health Research Ethics Board~~; hence, the procedures, standards, and requirements of the major research ethics committees are comparable.

~~The study was submitted to the UPMREB for review and was granted exemption from ethical review.~~ A total of 193 clinical trial protocols were included in the study. PTA information is explicitly required in protocol submission to the ~~UPMREB~~~~UPM-REB~~. The protocol template requires the investigator to indicate whether or not the protocol has ~~PTA~~~~post-trial access~~ provision stated in the informed consent document, with an option to indicate that ~~PTA~~~~post-trial access~~ is not applicable. To identify whether, for which drug type, and in what form PTA is provided, we gathered the following information from these protocols: ~~start~~~~begin~~ and end date of the trial, name of study drug, tested indication of the study drug, region the sponsor is from, type/category of the study drug, type of funding agency, provisions for PTA (yes or no), and the

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108 explanation for the provisions. From the Excel file, we then made a count of the number of
 109 protocols submitted to UPMREBUPM-REP per year, categorized the study drugs based on
 110 indication and the US new drug application (NDA) classification^c.

111 We ~~To know whether PTA is provided, we~~ counted the 'yes' responses on the question ~~whether the~~
 112 ~~trial provides PTA~~. We then collated their statements on PTA provision and categorized them to
 113 identify *in what form* PTA was provided. Lastly, to identify *for which types of drugs* PTA was
 114 provided, we grouped PTA provisions based on drug types based on indication and NDA
 115 classification.

116 Results

117 Number of trials and types of study drugs

118 The clinical trials were categorized based on the condition/disease that the clinical trial is
 119 studying. Most of the study drugs were meant to address non-communicable diseases
 120 (76.17%), most of which were for respiratory, neoplastic, and cardiovascular diseases (see Table
 121 1 below).

122 The 193 protocols, when categorized based on submission year, shows a downward trend in terms of
 123 submissions: 46 (24%) protocols were submitted in 2012, 39 (20%) in 2013, 35 (18%) in 2014, 32 (17%)
 124 in 2015, 26 (13%) in 2016, and 15 (8%) in 2017. These trials have varying durations ranging from less
 125 than 1 year to 9 years. Majority (75.13%) of the clinical trials range from 1 to 3 years (Table 1).

List of Diseases	Number of Clinical Trials
NON-COMMUNICABLE DISEASES	
Respiratory	30
Neoplasms	21
Cardiovascular	18
Mental/neurological	17
Autoimmune Diseases	16
Diabetes and Kidney	15
Pain	8
Musculoskeletal Disorder	6
Skin disease	5
Sense organ	3
Digestive diseases	2

^c The classification is as follows: Type 1: new molecular entity; Type 2; new active ingredient; Type 3: new dosage form; Type 4: new combination; Type 5: new formulation or other differences (e.g., new indication, new applicant, new manufacturer); Type 6: new indication or claim, same applicant; Type 7: previously marketed but within an approved NDA; Type 8: Rx to over-the-counter; Type 9: new indication or claim, not to be marketed under Type 9 NDA after approval; Type 10: new indication or claim, drug to be marketed under Type 10 NDA after approval¹¹.

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Genetic disease	2
Others	2
Urinary disease	1
Anemia	1
TOTAL	147 (76.17%)
COMMUNICABLE DISEASES	
Bacterial/viral (vaccine)	29
Other bacterial	11
Other viral	2
Fungal infection	1
Respiratory tract infection	3
TOTAL	46 (23.83%)

Table 1: Duration of UPM clinical trials

In terms of the condition/disease that the clinical trial is studying, most of the study drugs are meant to address noncommunicable diseases (76.17%), most of which are for respiratory, neoplastic, and cardiovascular diseases (see Table 2).

Condition/disease addressed by clinical UPM trials in UPM, 2012-2017

In terms of types of study drugs, most of the study drugs were new combinations, new molecular entities, and new formulations (see Figure 1).

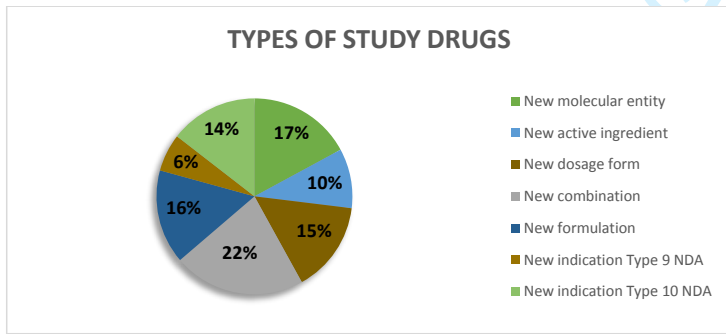


Figure 1: Types of study drugs in UPM clinical trials in UPM, 2012-2017

The clinical trials were predominantly sponsor-initiated studies from pharmaceutical companies in North America, Europe, and Asia (in descending order in terms of number of trials; see Figure 2). Note that no local trials were documented.

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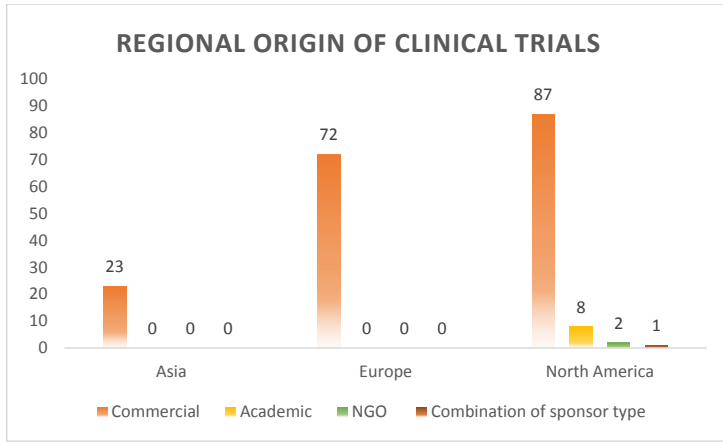


Figure 2: Sponsor origin of UPM clinical trials in UPM, 2012-2017

Post-trial Access Provisions

Among the 193 protocols reviewed from 2012 to 2017, 100 (51.81%) protocols indicated some form of post-trial provision, while 93 (48.19%) indicated that PTA is not applicable. The proportion of protocols with and without the indication of post-trial provisions remains approximately similar across the different clinical trial regional origins (Figure 3). This trend is relatively consistent throughout the years (Figure 4), in spite of the declining trend in clinical trial submissions.

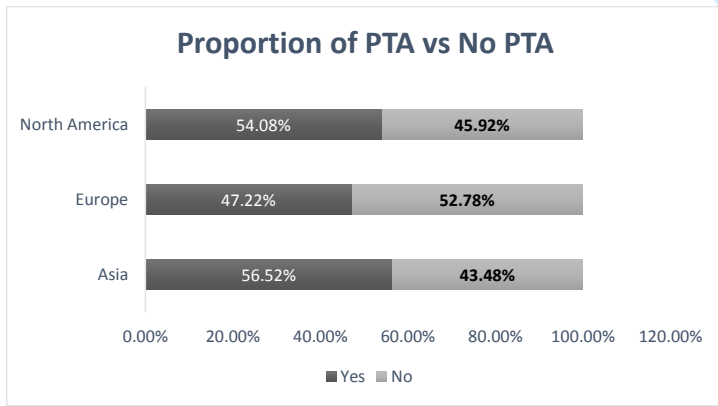


Figure 3: Proportion of clinical trials that indicated PTA versus those without a PTA indication

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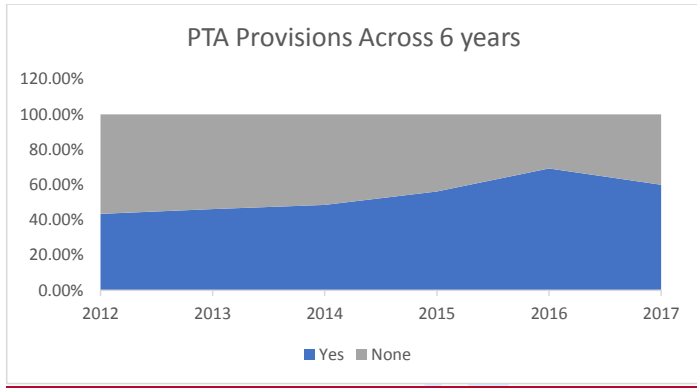


Figure 4: Proportion of clinical trials that indicated PTA versus those without a PTA indication, 2012-2017

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When these 100 protocols with indications of PTA were grouped according to type of study drug (Figure 5), the trend is comparatively somewhat similar to the total number of clinical trials grouped according to study drug type in Figure 1, i.e., most of the PTA indications were in new combinations and new molecular entities.

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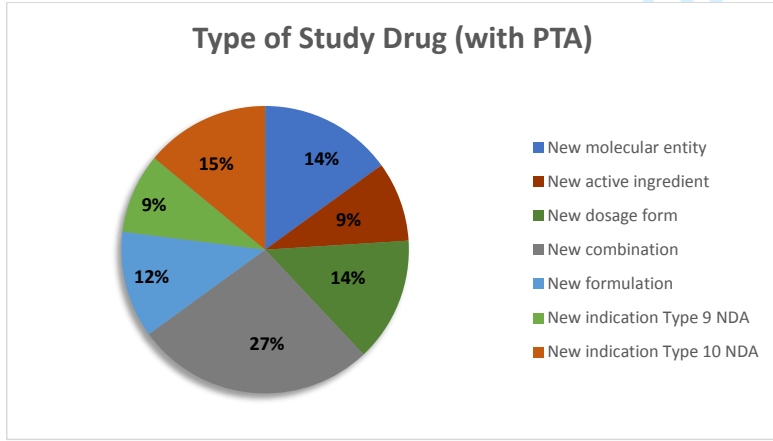


Figure 5: PTA according to type of study drug

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Among the protocols that indicated a post-trial provision, the PTA identified by the sponsors may be categorized as follows: (1) access to trial results (including registries) or information; (2) presence of standard of care outside the trial; (3) no PTA of the study drug will be provided; (4)

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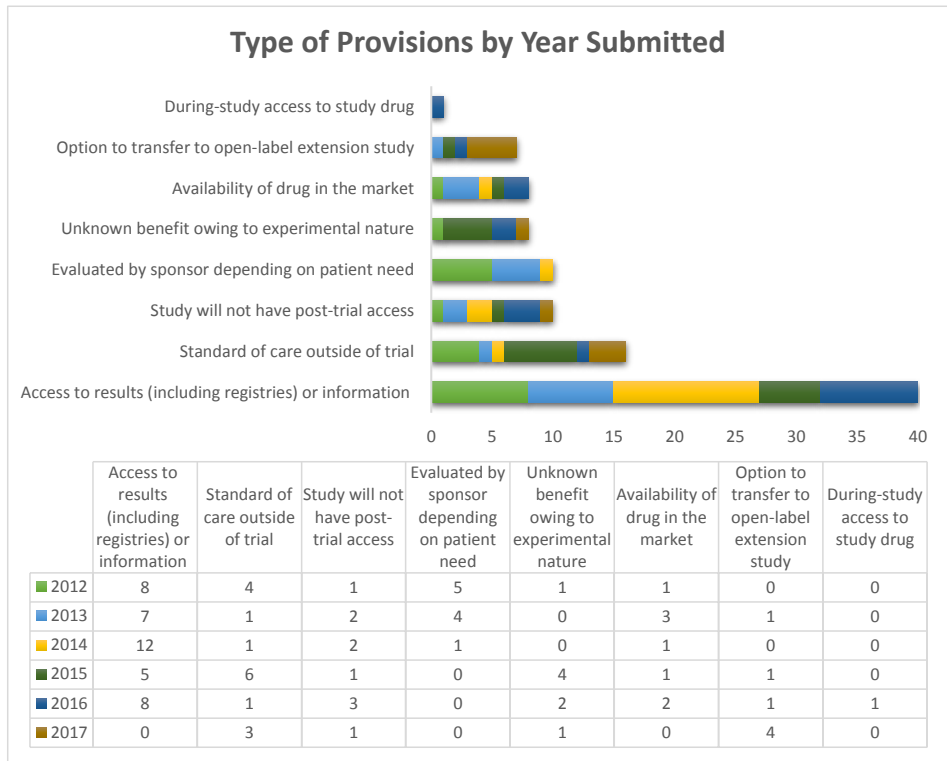
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164 PTA to be evaluated by sponsor depending on patient need; (5) unknown benefit owing to
165 experimental nature of the study; (6) drug will be made/is available in the market; (7) option to
166 transfer to open-label extension study; and (8) during-study access to study drug (Table 23).

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168 Table 23: Type of provisions by year of clinical trials submitted to UP Manila the UPM-REB.

170 In Table 2,3, we see that the most commonly common PTA indicated PTA is access to results,
171 including publication of results in a clinical trial registry or in medical journals, or the sharing of
172 information, including safety information and other information that could potentially be useful
173 in clinical decision-making. After access to information, the next commonly most common
174 indicated PTA is the availability of standard of care outside of the trial as an alternative to trial
175 participation. In practice, the IRB actively seeks the PTA provision only when the disease is rare
176 or incurable or treatment is very expensive, and only when the results are effective and safe.

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177 **Discussion**

178 The results of this study must be viewed in terms of the requirements of ethics guidelines,
 179 specifically of the Declaration of Helsinki and CIOMS, as quoted above. Helsinki requires the
 180 sharing of knowledge, practices, or interventions; however, this declaration is silent on when
 181 ~~what time of~~ PTA is relevant to which type of study. CIOMS provides more clarity in this matter,
 182 ~~specifically, that. Specifically, the latter requires~~ PTA is ~~(to be 1.)~~ the responsibility of the sponsor
 183 in cooperation with the government and other relevant stakeholders; ~~and (2.)~~ this
 184 responsibility consists in making the product developed ~~and~~ knowledge generated to be
 185 available as soon as possible to the population or community where the research was carried
 186 out.

187 The Declaration of Helsinki provision on post-trial access describes post-trial obligations as
 188 providing access to appropriate care or to relevant information after research [6]. In the
 189 literature, access to **appropriate care** has been interpreted to mean affordable access or
 190 “reasonable availability of beneficial pharmaceuticals or medical treatments” [12]; continued
 191 access to study interventions that have demonstrated significant benefit and for transitioning
 192 participants who continue to need care and preventive measures after the research to
 193 appropriate health services [13]; or an obligation to facilitate sustainable access or subsidized
 194 access to new interventions in host communities [14].

195 In our study, several of the types of declared PTA by the sponsors showed that some sponsors
 196 either have their own definition of PTA that is different from what ethics guidelines provide,
 197 different from what the literature refers to as appropriate care, or that the sponsors have no
 198 idea what ethics guidelines or the literature say about PTA. The following PTA categories are
 199 either not in agreement with the ethical definition of PTA or are directly opposed to it: (1)
 200 presence of standard of care outside the trial; (2) no PTA of the study drug will be provided; (3)
 201 unknown benefit owing to experimental nature of the study; (4) drug will be made or is
 202 available in the market; and (5) during-study access to study drug.

203 The literature suggests that the practice of providing PTA differs across countries and contexts.
 204 The example of Brazil and Argentina, for example, refer to PTA as access to the interventional
 205 drug of the patient participants after the trial and so long as they need it and before access to
 206 other means becomes available [8]. This type of PTA was not directly observed in our study,
 207 though the 5% (i.e., 10 of the 193) of the studies where PTA will be evaluated by the sponsor
 208 based on patient-participants’ needs *could* lead to this sort of access. At the same time, PTA
 209 may also mean the transition of the patient-participants into extension studies sponsored by
 210 pharmaceutical manufacturers until the intervention becomes available in the health system
 211 [13, 15, 16], though admittedly this is not always possible [17]. This was the case for 4% (i.e., 7
 212 of the 193) of the clinical trials in our study. Lastly, the provision of PTA may also mean
 213 incorporating in the trial design the continued access to a proven beneficial intervention (e.g.
 214 WHO recommendations that PTA, in terms of availability of the vaccine to the community, be a
 215 requirement before conducting a clinical trial on a respiratory syncytial virus vaccine in LMICs)
 216 [18]. This type of PTA was not observed in our study.

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217 The number of protocols that indicated PTA (51.81%) among the clinical trials reviewed
 218 seemed encouraging, at first. However, when we considered the types of PTA
 219 declared by the sponsors, we realized that the most that the population or community might
 220 get is information that may be clinically relevant in the future (40 protocols). In addition, there
 221 There were seven also the 10 protocols where the sponsor declared the future evaluation of PTA
 222 depending on patient need and another seven which might offer patient-participants the option to
 223 transfer to an open-label extension study, plus the 10 where PTA will be evaluated by the
 224 sponsor post-trial. In practice, sponsors provide post-trial access through follow-up studies to
 225 see long term effects on patients, open label extension studies, expanded access, and
 226 compassionate use, among others [9]. At best, these drugs are made available on a case to case
 227 basis [9] and not as a standard requirement to comply with the Declaration of Helsinki and
 228 CIOMS.

229 Out of the 100 protocols with post-trial provisions, there were 10 where the sponsor declared
 230 the future evaluation of PTA depending on patient need. This means that in all instances, *none*
 231 of the sponsors made PTA arrangements before the beginning of the study. Recall that CIOMS
 232 stipulates that before undertaking research in a community or population with limited
 233 resources, sponsors and investigators must “make every effort to ensure that any intervention
 234 or product developed, or knowledge generated, will be made reasonably available for the
 235 benefit of that population or community.” From the perspective of CIOMS, only the 40
 236 protocols that declared information sharing as PTA *partially* complied with the PTA imperative,
 237 and depending on how the sponsor decides on the situation, maybe the 17 others, too, who
 238 might consider PTA after sponsor evaluation or provide PTA in the form of an open-label follow
 239 up study. All others did not comply with PTA requirements at all.

240 According Second, several of the types of PTA that the sponsors declared shows that some sponsors
 241 either have their own definition of PTA that is different from what ethics guidelines provide, or that they
 242 have no idea what ethics guidelines say about PTA. The following PTA categories are either not in
 243 agreement with the ethical definition of PTA or are directly opposed to it: presence of standard of care
 244 outside the trial; no PTA of the study drug will be provided; unknown benefit owing to experimental
 245 nature of the study; drug will be made/is available in the market; and during study access to study drug.

246 Third, earlier we mentioned that according to another study, pharmaceutical companies mostly
 247 provide PTA in “exceptional circumstances” (i.e., the situation is life-threatening; discontinuing
 248 treatment would result to adverse effect on health of the participant; no local alternative
 249 treatment; and a positive benefit-risk balance of the safety-efficacy of the treatment) [9] (4).

250 Even when we narrowly define PTA this way, apparently none of the protocols saw the
 251 situation as exceptional enough to consider PTA pre-trial, and only 10 declared possible PTA
 252 subject to sponsor evaluation. This is a cause for concern because, first, at least some of the
 253 study drugs were meant to address diseases that could be life threatening such as the various
 254 kinds of neoplastic diseases or severe respiratory, autoimmune, or cardiovascular diseases.
 255 Second, we also know that a big proportion of the patient-participants of the UPM clinical trials

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256 ~~in UPM that~~ were likely to discontinue with treatment, especially for very costly drugs, for
 257 several poverty-related reasons: there is no universal access to health care in the Philippines
 258 and health care is usually out of pocket; poverty rate is currently at 21.6% [19] (10); and the
 259 Philippine General Hospital of the UPM, as a public hospital, usually caters to patients who are
 260 unable to afford private hospitals.

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261 Assuming that the study showed positive benefit/risk balance of efficacy-safety of the study
 262 drug, all the corporate indicators of what is “exceptional” seemed present in at least some of
 263 the studies. Since sponsors are usually aware of this situation, it must further be explored why
 264 none of the protocols considered PTA arrangements pre-trial, on the condition that there is
 265 positive benefit-risk balance of the safety-efficacy profile of the study drug, and only 10
 266 indicated this probability subject to sponsor evaluation. Literature offers to explain
 267 noncompliance to PTA. According to Wang and Ferraz, commitment to post-trial obligations
 268 may be onerous and may impede future research, regardless of who will be sponsoring these
 269 obligations, as it may redirect costs from funding other potential studies such as chronic and
 270 rare diseases [20]. Whether this reason holds from an economic perspective remains to be
 271 seen.

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272 ~~To As such, to~~ date, none of the clinical trial protocols evaluated by ~~UPMREB~~ ~~UPM REB~~ fully
 273 complied with ethical requirements for PTA. Through no fault of the IRB, there remains a lack of
 274 standardized governance to implement post-trial obligations [21]. If PTA is to be fully reflected
 275 in reality, clearly ~~more a lot of~~ work has to be done in terms of clarification of what the term
 276 means (i.e., what must be provided, in what manner, to what extent); ensuring common
 277 understanding of the term among the various stakeholders; a PTA-encouraging environment;
 278 and a structure that facilitates stakeholder cooperation for PTA.

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279 Conclusion

280 More than half (100 out of 193) of the clinical trials submitted in UPMREB indicated post-trial
 281 provisions and the most common post-trial access provision identified is access to information.
 282 Post-trial access will be dependent upon the evaluation of the sponsor based on patient need
 283 and the option to transfer to open-label extension study in ten (5%) and seven (4%) clinical
 284 trials, respectively. It can be deduced that none of the sponsors made PTA arrangements pre-
 285 trial, and at best, are made available on a case to case basis. This result is alarming since these
 286 clinical trials involved life-threatening diseases, and especially for researches conducted in
 287 LMICs where there is no adequate access to marketed drugs and even to universal health care,
 288 patients may not be able to access these drugs after the trial ends. As such, post-trial access to
 289 study drugs remains a challenge. There are existing guidelines stipulating post-trial obligations
 290 but there is poor compliance among the pharmaceutical sponsors. Furthermore, despite the
 291 CIOMS and Helsinki provisions on post-trial access, there seems to be no international
 292 consensus around it. Based on its current status, achieving post-trial access, as stipulated in
 293 ethics guidelines, would need further and considerable work. Of the 193 study protocols reviewed
 294 by UPM REB, 51.81% indicated PTA, but none of them fully complied with the PTA requirements as

295 stipulated in ethics guidelines. A lot of work needs to be done if PTA, as stipulated in ethics guidelines, is
296 to be fully reflected in reality.

298 Declaration

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300 *Framework Programme (FP7-PEOPLE-2013-COFUND) under grant agreement n° 609020 -*
301 *Scientia Fellows.*

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