Ethics Review in Anti-Doping Research: Experiences of Stakeholders

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Background. The World Anti-Doping Agency is the international body coordinating anti-doping efforts, with the mandate of harmonizing anti-doping policy worldwide. With novel performance-enhancing compounds continuously entering the market, research is necessary to develop appropriate methods for their detection. WADA-accredited laboratories are required to spend 7% of their annual budget on this research and need to obtain ethics approval for studies involving human participants. Nevertheless, these labs may face difficulties in obtaining ethics approval for anti-doping research due to its distinct differences from traditional biomedical research. Therefore, our aim was to investigate potential difficulties in obtaining ethics approval for anti-doping research.

Methods. Semi-structured interviews were conducted with stakeholders in anti-doping research to investigate their experiences towards the ethics review process of their research proposals. Interviews were transcribed, de-identified, coded and analyzed.

Results. The interviews indicated that large discrepancies in the evaluation of anti-doping research proposals exist. A majority of the laboratories could not acquire ethics approval for the administration of substances not approved for medical use. Some laboratories faced obstacles to obtain ethics approval for substances approved for clinical use. Respondents communicated that ethics committees are often lacking background knowledge about the anti-doping context.

Conclusions. Disapproval of research proposals may originate from concerns over the safety of the study, the fact that there is seldom a direct benefit to the participant, the consideration that volunteers may be incentivized to use prohibited substances, a lack of background knowledge about anti-doping or the focus of research ethics committees on health research.

Key words: anti-doping, ethics review, bioethics, ethics committees, doping in sports,

qualitative research

Introduction

The World Anti-Doping Agency (WADA) is the international body coordinating anti-doping efforts, with the mandate of harmonizing anti-doping policy worldwide (WADA 2019). WADA-accredited laboratories are responsible for carrying out testing of doping control samples. In addition, they are involved in the development of new analytical methodologies for doping control. The International Standard for Laboratories (ISL) requires WADA-accredited labs to spend at least 7% of their annual budget on research activities in support of doping control, generally defined under the label of "anti-doping research" (hereafter "ADR") (WADA 2016, 24).

These research activities are of paramount importance to keep up with emerging doping techniques, such as the use of new performance-enhancing substances by athletes to gain a competitive advantage in sports. As such, anti-doping authorities often seize substances not approved for human consumption (e.g. designer drugs or veterinary-class drugs) intended for doping use. Furthermore, substances approved for medical use, such as EPO and diuretics are also regularly misused for doping purposes. Problematic to anti-doping researchers is the continuous flow of potential performance-enhancing substances exiting the pharmaceutical pipeline and entering the (black) market. Doping athletes are always in competition with anti-doping researchers, as they are driven towards those products which they perceive as the least detectable while anti-doping researchers have to respond quickly to the use of those (novel) products that cannot be easily detected (Sottas et al. 2011). ADR starts with the elucidation of the pharmacokinetics, metabolism and clearance of these drugs, with the goal to develop such methods. Without keeping methods up-to-date with contemporary doping threats, athletes would find at their disposal numerous drugs that would allow them to transgress anti-doping rules with a low probability of incurring an anti-doping rule violation, thus violating fairness

in sport. Moreover, without efficient detection methods, athletes might not be deterred to use substances potentially at the detriment of their health.

In doing ADR, the ISL requires that laboratories comply with *"the Helsinki Accords and any applicable national standards as they relate to the involvement of human subjects in research"* (WADA 2016, 89). This means that when carrying out research that involve human subjects, WADA-accredited laboratories have to go through a process of ethics review by a designated Research Ethics Committee (REC). However, laboratories may face difficulties in obtaining ethics approval from RECs due to the significant differences that set this research domain apart from traditional biomedical research.

First, while traditional biomedical research mainly deals with the administration of compounds in the pharmaceutical pipeline to human subjects with the *objective* to verify endpoints such as safety and efficacy, ADR is focused on evaluating potential performance-enhancing effects or metabolism of substances, and the subsequent development of methodologies for their detection in biological matrices.

Second, the study design may differ substantially from traditional biomedical research as, amongst others, sample sizes are generally small, participants may be recruited from often atypical populations, substances that are administered are not always used for medical purposes, and the protocol (e.g. micro-dosing) may not be similar to those used in a medical setting.

Third, researchers may face difficulties in collecting reliable preclinical information. In particular, limited evidence on the safety of non-approved substances exists, and the evidence that may be used to support administration studies in humans, such as information of high-dose use collected from body builder websites, does not have the level of scientific evidence that is expected. Performing pre-clinical studies for all non-approved substances used as

doping agents might be unfeasible in terms of resources (e.g. available personnel, financial costs) for individual labs. Furthermore, it must be noted that no financial return on investment exists in this setting as in the pharmaceutical field, as the goal is not to ultimately market substances. As for substances approved for medical use, doping scenarios almost never consist of the administration of a single therapeutic dose and, therefore, the accurate modeling of these situations in volunteers is more difficult.

Drawing from the requirement, set forth by WADA and directed to WADA-accredited labs, to conduct ADR compliant with national and international ethics standards, *vis-à-vis* the difficulties in obtaining ethics approval due to the aforementioned differences between ADR and traditional biomedical research, the goal of this study is to identify the experiences of stakeholders, within the field of ADR, with regard to ethics review of their research proposals.

Methods

Qualitative research methods were used to explore the experiences of stakeholders in the field of ADR. Members from WADA-accredited laboratories, International Federations (IFs), National Anti-Doping Organizations (NADOs) and WADA were recruited to participate in interviews using a sampling strategy that aimed to identify individuals with experience in ADR. Additionally, a list of contact persons of interest was acquired *via* a contact person within WADA. Snowball sampling was also used in order to allow participants to nominate other potential stakeholders that could be interviewed.

Seventeen stakeholders in ADR were contacted and requested to participate in the study. Ten stakeholders in total agreed to enroll in the study. Eight were lab members recruited from WADA-accredited labs on four continents. Interviews were semi-structured and were audio-recorded, transcribed *verbatim*, de-identified and analyzed using inductive content analysis in

which content categories are derived from the data collected during interviews, rather than using pre-determined categories (Downe-Wamboldt 1992; Graneheim and Lundman 2004; Schamber 2000). All transcripts were coded into broad content categories. Sections of the data within the broad categories were compared and more specific subcategories were developed, when necessary. As interviews were conducted through Skype, respondents provided their informed consent orally after having been informed about the purposes of the study in written. The study was approved by the Research Ethics Committee .

Results

The data collected during the interviews were classified into the following categories: (1) general experience with RECs' ethics review process; (2) international discrepancies in ethics review; (3) research participants in anti-doping research; (4) ethics approval for the administration of non-approved substances; (5) ethics approval for the administration of substances approved for clinical use; (6) options to facilitate obtaining ethics approval.

(1) General experience with RECs' ethics review process

Overall, respondents stated that in their experience RECs are more accustomed to evaluate projects designed for the development of novel pharmaceutical compounds or health-related research more broadly, but are less familiar with ADR. Therefore, various respondents argued that RECs might lack an appropriate understanding of the anti-doping context. As a respondent elaborated:

> *We presented approvals to the ethical committees and in all cases, we were invited to be interviewed and to present the project in order to specify the aim very clearly. The ethical committee is not an anti-doping ethical committee. I would say it is a pharmaceutical ethical committee. They are usually dealing with new therapeutic strategies to treat disease and to also think of having clinical studies with 300 or 3000 subjects and when they receive a weird project with, for example, a minimum of 6, a maximum of 12 subjects of both sexes, they say: "What is this? Let us ask the principal investigator. (Interviewee 5)*

In general, respondents felt that their RECs were overly strict, but recognized that RECs should consider the risks to which research participants are exposed. Nevertheless, the respondents also argued that the use of substances for performance/image-enhancing purposes are used by many people, thus representing a public health problem and worthy of deeper consideration.

> *I can understand [the ethics committees] because for medications that are [only] approved for veterinary use, I do not know the risk and they do not know the risks so if the risk has not been measured in humans, they cannot accept that these drugs are given to humans. The risk as a limitation is reasonable but nevertheless we need these studies. For new designer drugs that appear on the Internet every day; this is the same situation. These are drugs designed to have stimulant effects and to study the effects of these drugs in the population, not only to look markers for the detection of drugs, we need to have ethical approval to administer these drugs in healthy volunteers. It is not only a problem of the doping control world; I think it is a public health problem. Plenty of people are using these drugs so we need to study the pharmacological effects on healthy volunteers and to study the toxicity of these drugs, even if they are not approved for medical purposes. We have to find a solution to study this type of drugs. (Interviewee 1)*

(2) International discrepancies in ethics review

Most respondents also acknowledged that RECs worldwide do not handle research proposals in the domain of anti-doping in the same way. In contrast to other researchers, some respondents expressed that they were not able to receive ethics approval to administer drugs that were not commercialized in their own country. Some respondents described that in some countries no excretion studies could be done with contaminated supplements, but that others were able to perform such studies. Other respondents described that some labs were able to get an ethics approval to perform a single-dose, single-person administration study while others were not.

> *I know that other people have had challenges with administration of prohibited substances. (…) Steroids or narcotics or those types of drugs that are not always approved for human use… Those can be particularly problematic to get IRB approval for and I have heard of situations where organizations or investigators may have to go to a different country in order to get those approvals or they may have to modify the way they are designing their experiment in order to get the approvals. (…) Some*

> *laboratories have more troubles than others in getting a blanket approval to do single-person administration studies. I know some laboratories are able to do an n=1 experiment with a single dose administration. (Interview 2)*

Multiple interviewees co-operated with other laboratories in order to facilitate obtaining ethics approval.

> *[Here], the ethical committees are very strict and I do not know how to solve it. I will keep co-operating with other laboratories whose countries have more flexible ethical committees. (…) I have seen that (…) some other groups have much less problems. They have no problems in getting approval of (…) huge doses of drugs. This is the individual variability among countries. (…) All the excretion studies we have available come either from the WADA or the WAADS (World Association of Anti-Doping Scientists), in which apparently there are some countries or laboratories that are more free to perform excretion studies. (…) I would be never able to do here in because they are new drugs or drugs that are still under approval. I can do an excretion study of for example, ibuprofen or even of testosterone on a patient, no problem. (Interview 5)*

Various respondents acknowledged that there is variability in ethics review of studies between countries, where RECs in some countries are more flexible to approve for example excretion studies of non-approved drugs or studies in which autologous transfusions or high doses of drugs are administered. Some respondents expressed that this compelled them into collaborations and to perform studies in countries where ethics approval could be received.

> *We have collaborators all around the world and sometimes we shared the load. In [country A], they will administer everything because they are very liberal there. [Country B] was a little less liberal but more liberal than [here]. Our local collaborators in [this country] cannot get anything approved, their ethics committees are very strict. And the local university has been decent, they are relatively liberal but our biggest issue is that they are very slow. (…) I feel that there are large inter-country differences, absolutely. In [country A], they did a study for us on some of these steroids that are not approved. Apparently, they can do an n=1 on anything they want. (Interview 9)*

Due to the differences in the ethics review processes, some participants suggested that some form of harmonization would be useful. One participant argued that, within the EU, regulations are stricter than elsewhere.

> *Maybe some harmonization between the ethical committees between the countries might be good. (…) There are countries where the ethical rules are better in place*

than in other countries. I would say that within Europe, the regulations are quite well harmonized and relatively strict and really protecting the individual and that means that in practice, the ethical approval might be difficult to be granted in cases. (…) And some ethics committees [in other countries] are a little bit less critical. (Interviewee 3)

(3) Research participants in anti-doping research

Various respondents explained that recruiting research subjects is difficult. The unknown safety profile of many substances, and the time that needs to be dedicated to participation were mentioned as the principal reasons for refusing participation or withdrawing from the study.

Recruitment of volunteers is quite a difficult process. They always ask: "What if, what if, what if…" And, in many cases, you cannot answer this because, for most of these substances, you do not know what the proper safe dose is, you do not know what the appropriate use is and, in many cases, there are no guarantees. And we have had people who had withdrawn after agreeing, and then they come and they say "No, we changed our minds". (…) In one study, we were only able to find eight participants. (…) We aimed for more but (…) there were so many blood samples taken from them as well as urine. Many of them did not like the protocol and did not want to go through this. We had some studies with higher numbers. It depends on how much time they need to commit as well. Some of them would not mind taking the substance but they do mind the time they have to commit. (Interview 7)

As recruiting healthy volunteers might often be difficult, various laboratories would try to recruit from a patient population, who would normally receive the substance of interest to treat a pathology.

We use patients to prove our hypothesis. If we see that the hypothesis is working, we try to do the same with the patients of the same age and status as elite athletes. (…) For some of the ways of administration, it is very difficult to obtain ethical approval with healthy volunteers because this administration can potentially cause damage. So, to study this, we use patients that need to be treated with these substances in these administration routes. (…) For all of these samples, we would receive ethical approval and the subject gives the consent to participate in the study. (Interviewee 1)

Some respondents also expressed that healthy volunteers have often been recruited from among the lab personnel, because they are certain these people are not using other prohibited substances and they can be relied on to stay clean.

> *Historically when we had ethics approval, it was normally a member of staff who would do the excretion study. (…) Normally we would ask for volunteers within our staff because we know they are not taking anything else. And if we try to recruit from outside, the volunteers we normally find are high-risk people for taking other things. So, we have to pre-screen them to make sure they are actually clean and then give them something and we cannot rely on them to stay clean. (Interviewee 4)*

In certain cases where it would not be possible to get an ethics approval to administer certain substances to healthy volunteers, the option to study substance users retrospectively was considered. For example, some body builders report on blogs on products that they have been using. However, this setting is not well-controlled and the quality and dose of the products that were taken cannot be tested. Moreover, respondents were also concerned that more active collaboration with such groups could also be considered as inciting to use prohibited substances.

> *If bodybuilders are using naturally, no IRB is going to say: "Yes, go ahead and use the bodybuilders just because they are crazy and stupid." (…) We have thought of going in that population [to study intake of these substances retrospectively] because they describe what they are taking, how often they are taking and so forth. (…) They will inject anything, not knowing exactly what it is. They think they know what it is but when we test some of these products that are seized, they are not always what they say they are. So, the problem is we could have bodybuilders saying they are doing three times a week of boldenone injections and it may not be boldenone. The problem we have is it would never be controlled unless we gave them the drug and then we are back again to the problem again [of needing ethics approval]. (…) The only way we thought we could get around that was if we offered free testing of their products. But we could not pretend we were not involved then, knowing that they are then going to inject them and then collecting urine. I think an IRB would consider that we are heavily involved in that project.* (Interviewee 9)

Some respondents also noted that there is always the concern that research participants might get motivated to use the substances and that there might be implications if that person wants to move into elite sports. Persons who already use the substance could be an alternative, although their metabolism might differ because of long-term substance use.

> *It is using doping substances, even if it is an amateur. Maybe they get interested in using it. You do not know the volunteers you recruit. I understand the principle why they would be very cautious and especially with steroids, it is can be a long-term effect. What if the person wants to become an elite [athlete]… At the same time for us it is very different to use a person who has been using steroids for decades. Then*

> *probably, the body already has an advantage so you are adding more and what is going to happen, even if you withdraw the person, it is just not the same. So, we accepted it, but we know that the results are not going to be the same. The outcomes are going to be different from an athlete who goes professional and starts doing steroids. (Interview 6)*

(4) Ethics approval for the administration of non-approved substances

The majority of the study participants reported difficulties to obtain ethics approval for studies where non-approved substances are to be administered to healthy volunteers. Respondents noted that certain doping agents (for example some anabolic steroids) are commercialized for veterinary use only, and that it is very difficult to obtain ethics approval for administration in humans. One respondent argued that the administration of non-approved substances is problematic within Europe and mentioned one case where no ethics approval could be received for an excretion study with an anabolic steroid. This defeated the purpose of the study, which was to recreate metabolites of this substance *in vitro*, which was intended to be used as reference material for methods of detection.

> *Everywhere in Europe, the administration of substances which are not approved by the European Medicines Agency for clinical use is a complex issue. (…) We wanted to have an excretion study done with metandienone, which is an anabolic steroid, because we were capable of producing them with enzymes in vitro. We wanted to have a human sample for comparison but because metandienone was at that time not available as a pharmaceutical product within the EU, we did not get an ethical approval for that. (…) The whole idea of the project was to be able to [ultimately] avoid human studies but to make sure that the simulation is equal to the human administration, we need to have samples to compare with to demonstrate this in vitro model. (Interviewee 3)*

Some interviewees stated that to be able to perform an n=1 study with non-approved substances would help out the lab and anti-doping researchers in general. However, respondents also acknowledge the difficulty of getting such studies approved.

> *One thing the ethics committee is really strict on here, and that could really help us if we could do it, is to do an n=1 for an excretion study of steroids that are not approved [for medical use]. Think about the scandal coming out of Russia with the oral turinabol... We cannot do an excretion study with that, even as an n=1 to see what metabolites are coming out because it is not approved. (…) The only way that*

> *we have been told we can do these studies is if we apply for a new drug discovery. Which is basically the same application as a pharmaceutical company does to administer one of their new drugs, and that costs millions so that is never going to happen for us. (Interviewee 9)*

Two respondents indicated that they were able to perform excretion studies with contaminated supplements after review of the safety profile.

> *We also do smaller studies because in some cases we cannot buy reference materials. We would need to do an excretion study and we might only give a single oral dose to one person so that we have something that we can use as a part of our reference collection to confirm doping violations in athlete's samples. (…) Where we have approval to access the product we want to do an excretion study with and we have reviewed the supplement and analyzed it… If we know it is relatively clean, it is only got the particular substance in there and it does not have side reaction products and we think that the substance is not going to be dangerous from information that we can search on from the internet. Then we did that review and then we provided the information to the ethics committee and they would approve us to do a single oral dose of the supplement. (Interviewee 4)*

To solve the problem of elucidating the metabolism of non-approved substances, some respondents argued that *in vitro* or *in vivo* models could be used. However, in those cases, reference samples coming from human administration would still be necessary for comparison purposes. As an alternative, positive doping control samples could be used. However, positive doping control samples only offer a cross-section of the metabolism of a drug (i.e. at one timepoint) and the dose, frequency of use and the time since the last administration are unknown. Therefore, the uses for these samples are heavily limited as an alternative to administration to healthy volunteers. One interviewee suggested recruiting as research participants those who are using the particular substance of interest. Moreover, this respondent also suggested that administration studies could be performed in a specialized environment to adequately control health risks.

> *It is possible to find some solutions. For psychoactive drugs, probably the solution is to approve studies on people that are using these types of drugs. (…) For doping control, it is difficult to find, for example, athletes using boldenone. No one will tell you that they have used boldenone in the past and they are ready to participate in a study of boldenone because we are interested in studying the metabolism of boldenone. (…) Normally these studies are performed under medical supervision for*

> *maybe 24, 48 hours and if they are controlled, it can be done [safely]. (…) Probably these studies have to be performed on people in centers with persons specialized in these types of drugs. If people are specialized in psychoactive drugs, although there is a new one, if they have experience with others [of the same type], probably the risks are known better and maybe they can be better controlled. For this reason, we need a global solution in the anti-doping field. We cannot think that each lab will find a center that has experience doing these types of studies. (Interviewee 1)*

Another interviewee shared the vision that it may be an option to conduct such studies in countries where RECs allow them, although emphasized that this should never result in "shopping around for approvals".

> *I do not like shopping around for approvals to circumvent safe regulation just because a country does not care or does not know any better. I am not a real fan of doing that. However, some of these things I would consider relatively low risk and if it is very strict in a certain country for whatever reason and it is a low risk study, then I am for it. In the right circumstances, I think its fine to do it somewhere but not at the cost of hurting individuals. (Interview 9)*

(5) Ethics approval for the administration of Substances approved for clinical use

Aside from difficulties in obtaining approval for non-approved substances, some respondents reported experiencing limitations to perform studies with approved substances. One interviewee stated that supratherapeutic doses for anabolic steroids and studies in female populations are problematic in ADR, and that such protocols cannot be easily justified to RECs.

> *If the doses are higher than the recommended therapeutic doses, which are often used for the doping purposes, then the ethical approval is extremely difficult to get. Normally, in my experience, [they request] a single therapeutic dose and this almost never is a doping scenario. (…) Taking micro-dosages of EPO over a certain time period… This is not practically very easy to justify or administering large doses of anabolic steroids… You will never get ethics permission for that. Or administration in female populations, this is in my opinion one of the critical things. (Interviewee 3)*

Another respondent discussed that ethics approval is difficult to obtain if there is no clear benefit envisaged. Moreover, the same holds if the drugs are commercialized elsewhere in the European Union but not in the home country, or in case of medications commercialized outside the European Union.

> *There are some limitations [to research on healthy volunteers]. For example, it is very difficult to receive ethical approval if the benefit of the study is not clear for the volunteer. In the case of intra-articular administration, the ethical committee considers that this may cause damage to the health of the volunteer so it is very difficult to have ethical approval to do this kind of administration in healthy volunteers. But, they let us use samples from patients that need to be administered in this way. (…) Another important limitation is that for all drugs available on the Internet, it is very difficult to obtain ethical approval to use them because they have not been approved for human use [in this country]. It is very difficult but we can obtain permissions to use medications approved within the European Union, even if they are not used [here]. The process is very long but in some cases we have succeeded in obtaining these permissions. More difficult is to obtain approval for medications commercialized in the United States. To import the medications, you need to have companies specialized in importing this type of medication. (Interviewee 1)*

Another respondent communicated stringent treatment of research proposals by the local RECs, claiming that only patients could be recruited in experiments they envisaged, and not healthy volunteers. The same interviewee reported also that approval for drugs not commercialized in the home country could not be received.

> *My experience is that here [in my country], it is already very difficult if the volunteer is not a patient. I could get an approval if the volunteer really needs the drug and so (…) we do not administer a pharmacological active compound to a person that does not need it. It is very seldom the case [that we administer substances to healthy volunteers] and when it is the case, if we have 2 or 3 volunteers, these are already great results for us. (…) Here, we cannot study a drug that is not approved [in this country] so if I want to study a betablocker that is approved in Mexico, I cannot administer it to volunteers. (Interviewee 5)*

(6) Options to facilitate obtaining Ethics Approval

Multiple respondents made clear that more dialogue is needed between RECs and anti-doping researchers, and that the uniqueness of ADR should be made clear. It was argued that a meeting between RECs involved in the evaluation of ADR proposals could be productive. In that occasion, discrepancies in ethics approval and requirements for ADR could be discussed. The same interviewee suggested that WADA could potentially guide RECs, clarifying which technical requirements related to the protocol have to be fulfilled for study's approval.

> *Maybe we should have also a meeting for the ethical committees. (…) I think it could be nice to know which are the fundamental criteria that other ethical committees consider as something necessary to approve a project. (…) WADA did a lot in harmonizing the criteria for ISO17025-accreditation. (…) I do not know if WADA can do the same with some guidelines for ethical committees. To say: "These are the conditions for which you should reject the study". If the ethical committee then verifies that there are no health risks or privacy risks, then they should be suggested to approve the project. (Interviewee 5)*

One respondent argued that WADA could also help by writing a formal letter of support of ADR, which could facilitate ethics approval. Such a letter should point to the scientific relevance of ADR for doping control testing.

> *In order for our research to be acceptable, we have to prepare our research plan according to the policy of our ethics committee. If WADA would cooperate in expressing views with letters or documents strongly indicating the importance of the research, it may be possible to conduct research on more appropriate content. (Interviewee 8)*

Conversely, other respondents clearly advanced that WADA could not intervene in the REC decision at a local level. However, one respondent suggested that WADA could identify countries and/or centers where excretion studies with non-approved substances could be performed.

> *If I am trying to seek ethics approval from my local ethics group, I do not think WADA can really help. From a laboratory point of view, it would be probably helpful if WADA did excretion studies of things that are difficult for us to get a hold of and then distribute it to all the labs. That would be helpful. (Interview 4)*

Discussion

Undergoing an ethics review process is a mandatory requirement for conducting proper (clinical, medical, health related) experimentation on human subjects. The need for ethics approval expands also to non-medical human-subject research, such as research conducted in sport and exercise sciences and forensic sciences, within which ADR is located. In this article, we discussed the experiences of anti-doping researchers when submitting their research proposals for ethics review. In general, respondents felt that RECs are more used to

evaluate projects for the assessment of novel pharmaceutical compounds for medical use (i.e. clinical trials) and health research, but that they are less familiar with ADR.

Respondents reported that acquiring ethics approval is particularly difficult in case of the administration of non-approved substances to human participants in order to study their metabolism. This category includes the following: substances formerly approved for medical use; substances suited only for veterinary use; substances which arguably have been developed specifically for doping purposes (e.g. designer steroids); substances which are still in the pharmaceutical pipeline but are available on the black market; and drugs for which clinical testing was discontinued. No or little information may be available about the performance-enhancing effects or toxicity of these products as they might not have gone through the rigorous *in vitro* and *in vivo* and clinical testing process that compounds in the pharmaceutical pipeline are subjected to. As these products are used for doping purposes, there is a need for researchers and the anti-doping community to study their metabolism and to subsequently develop methods of detection for these products. However, respondents experienced in many occasions not to be able to perform excretion studies with non-approved substances. One way to study the metabolism without having to administer these substances to humans is to use *in vitro* (e.g. human liver microsomes) or *in vivo* models (e.g. humanized liver mice) (Lootens et al. 2009, Esposito et al. 2015). Nevertheless, in such cases, a human reference is always necessary to compare these models with the human metabolism. Another way to study their metabolism would be in matrices from individuals who make use of those substances outside of a research context, namely substance users. On this point, it must be noted that the broad group of "substance users" referred to in this paper is heterogeneous, as it might include individuals that use substances for various reasons (e.g. muscle-enhancing purposes). Notwithstanding, this brings its own scientific as well as ethical challenges. On the one hand, long-term and/or high-dose use of substances in individuals who may take other

drugs concomitantly does not seem comparable with the situation of athletes. On the other hand, including substance users in research studies might incite them to use prohibited substances. Scientifically speaking, in those cases where *in vivo* or *in vitro* methodologies are inadequate, n=1 (single dose) experiments with healthy volunteers might be the most appropriate way to generate reference materials of drugs. Nevertheless, sufficient safety information (e.g. via screening of supplement for side products, pre-clinical information on toxicity) and risk management strategies should always accompany such experimentations.

As doping athletes clearly do not follow standard medical practice, the risks of their doping habits may be relatively unknown. This results in the situation where the external validity of experiments might be called into question if they solely follow standard medical practice (e.g. the administration of insulin in diabetes patients) yet replicating exact doping regimes would be criticized since the REC may consider that such experiments bear unknown or too much risks. Here, the balance between comparability (or validity) and risk should be considered. Ideally, an experiment should be as similar as possible to doping regimes, within the boundary of justified and reasonable risk (CIOMS 2016). Beyond this boundary, scientists might have to resort to studying similar interventions in a medical setting or invest substantially in adequate risk-management strategies (supervision, follow-up, pre-screening of participants).

Various respondents reported that intercountry differences exist with regard to ethics review of ADR studies. They pointed to the fact that some laboratories were able to perform excretion studies with non-approved drugs, possibly in the form of contaminated supplements, thus being able to generate reference materials for these substances. However, discrepancies in the ethics review process of research proposals amongst RECs located in different countries are not limited to ADR, and even intra-country disparities exist (Edwards,

Stone, and Swift 2007, Monica Taljaard 2014). Indeed, despite existing international Declarations and Guidelines, the proper way of balancing – as well as of interpreting and applying – ethical principles may differ from committee to committee, thus leading to heterogeneous answers depending on the REC consulted. However, in many countries, ethical guidelines and policy documents have been enshrined formally into national law, partly standardizing aspects of intra-country review processes. Differences in handling research proposals should be an area of concern for the international research community, as this might undermine the purpose of the ethics review process, which is to protect research participants against harm.

We can surmise several reasons for these discrepancies. One explanation may be that WADA-accredited labs are dispersed widely across the world. Thus, cultural sensitivities as well as different legal frameworks might heavily influence the outcome of the ethics review process. Moreover, as stated before, RECs might not be familiar with ADR. Additionally, RECs members' sensitivity as well as research ethics guidelines they are familiar with, are based (almost exclusively) on biomedical or more broadly on health-related research. Presently, the Standard for Sport and Exercise Research is the only document that addresses, albeit briefly, research involving doping agents (Harriss, Macsween, and Atkinson 2017).

During the interviews, it was mentioned that healthy volunteers would regularly be recruited among lab personnel. Although lab personnel may be considered as a vulnerable population, this option is justified by claiming that the former are familiar with the protocol of ADR, thus being trusted to follow it strictly, and that no formal (and potentially arduous) recruiting process needs to take place (Ripley 2006; CIOMS 2016). Moreover, when persons are recruited from outside the laboratory, the lab could attract volunteers who may use prohibited substances prior to enrolment in the study, influencing the outcomes of the experiment.

Moreover, individuals might be incentivized to dope after the termination of the study. Although justificatory reasons underlie the enrolment of lab personnel, it remains important to consider whether such recruitment could be subject to undue influence because of a superior-subordinate relationship (CIOMS 2016, 58). Alternative recruitment methods might be considered, and clear procedures should be put in place to avoid undue influence.

Another topic that was briefly discussed during the interviews was the risk-benefit ratio in ADR projects. As some respondents noted, risks involved in ADR is often unknown, and, even when known, the risk-benefit distribution might be unfair for the single healthy volunteer enrolled in the specific anti-doping study. Indeed, the population which may turn out benefiting from ADR – namely athletes – are not a group of research subjects that can be enrolled. In our view, this sort of "intrinsic inequity" characterizing ADR should not prevent, in itself, from allowing the conduct of research in this area, even when vulnerable populations are enrolled.

Concerns about recruiting healthy volunteers can partly be solved by including patients, which was the option adopted by some labs associated with a university or university hospital. The key advantage of enrolling patients is that the administration of those substances which are registered as medicines or are used off-label may benefit the patients themselves, thus partially filling in the aforementioned gap. Respondents who performed such studies stated that this represented the most acceptable scenario for RECs, thus allowing ethics approval to be obtained relatively easily. Besides ethical advantages, there are, nevertheless, significant scientific disadvantages related to such an approach. For example, the patient population does not closely resemble the population of elite athletes as the metabolism of drugs is subject to age-related changes (e.g. reduction in hepatic and renal

clearance) and the training status of the individual (Somani 1997, Mangoni and Jackson 2003). Therefore, the research outcomes may not be representative for the athlete population.

Conclusions

ADR is paramount to maintain the functionality of the doping control system. This study strongly indicates that substantial discrepancies in the ethics review processes of ADR projects exist. We report that some labs encounter difficulties in receiving approval for studies with healthy volunteers, possibly resulting from concerns over the safety of the study, the fact that there may not be a direct therapeutic benefit resulting from the study, the consideration that volunteers may be incentivized to use prohibited substances, the lack of background knowledge about the anti-doping context or the focus of research ethics committees on health research, which may lead to ADR being comparatively less appreciated. A majority of the labs declared not to be able to perform studies involving healthy volunteers with substances not approved for medical use. Some labs reported difficulties to obtain ethics approval for the administration of substances approved for medical use to healthy volunteers.

In any case, for the continuous anti-doping effort in sports to be most effective, a framework is needed where new analytical methodologies are swiftly introduced into anti-doping practice in response to the identification of new potential doping substances in the pharmaceutical pipeline or on the (black) market. Properly understanding potential difficulties with regard to the ethics review of ADR will be crucial to avoid undue disapprovals of research proposals and to ensure that research can be carried out in a timely manner. Future research should aim to discuss in-depth the applicability of several existing ethics guidelines, to devise ethics principles applicable to ADR and to discuss specific (and potentially unique) ethical issues related to ADR. An inclusive approach should be taken

towards research coordination to assure full comprehension of the pipeline of ADR projects, the concrete needs of the ADR community, study design of projects and other crucial aspects such as available resources and the legal framework. We envision this would maximize the applicability of the future guidelines.

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Disclosure of Interest

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