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TITLE: *Anti-doping research and the Helsinki declaration: (mis)match?*

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ABSTRACT

The fight against doping in sport is internationally coordinated by the World Anti-Doping Agency (WADA). Through its World Anti-Doping Code, WADA aims to harmonise anti-doping policies, rules and regulations. One key reference document bound to the Code is the *International Standard for Laboratories (ISL)*, which mainly specifies the criteria that must be met for laboratory accreditation, as well as standards to adopt for the production of valid test results and evidentiary data. Within the ISL, the *Code of Ethics* refers to the Helsinki Declaration as a guiding framework for anti-doping research. However, inasmuch as anti-doping research structurally differs from human subject research as considered by the Helsinki Declaration, the applicability of the latter to anti-doping research can be called into question. In this work, we discuss how key principles of the Helsinki Declaration apply to anti-doping research and highlight frictions, incompatibilities and misalignments. Furthermore, we indicate possible solutions for operationalizing the principles within the context of anti-doping research.

KEYWORDS

ANTI-DOPING RESEARCH, RESEARCH ETHICS, BIOETHICS, HELSINKI DECLARATION

Anti-Doping Research and the Helsinki Declaration: (mis)match?

1. INTRODUCTION

The fight against doping in sport is internationally coordinated by the World Anti-doping Agency (WADA). Through its World Anti-Doping Code (WADC), WADA aims to harmonise anti-doping policies, rules and regulations within sport organizations and among public authorities across the world (WADA 2005, 123). WADA oversees and works in cooperation with a network of stakeholders, such as International Federations (IFs), National Anti-doping Organizations (NADOs), the International Olympic Committee (IOC) and national governments.

Laboratories which aim to conduct doping analysis of athlete's samples coming from doping control must first receive accreditation from WADA. The *International Standard for Laboratories* (ISL) and supplementary technical documents outline the procedures to receive accreditation. WADA-accredited laboratories must adhere to the Anti-Doping Code, the International Standards and the related technical documents. Aside from routine testing, laboratories are also engaged in anti-doping research, which must account for 7% of their total annual budget (WADA 2019, 29). Anti-doping research could include various activities, such as the development of new methodologies to detect prohibited substances or methods, the improvement of existing methods, research on physiological thresholds of endogenous substances influenced by doping use, the refinement of the Athlete Biological Passport¹ to detect doping use via their impact on blood and urine variables, or development of *in vitro* or *in vivo* methodologies to predict (minor) metabolites of illicit performance enhancing drugs.

In order to promote anti-doping research worldwide, the World Anti-Doping Agency (WADA) also sponsors specific research projects with annual grants. Other organizations, such as the Partnership for Clean Competition (PCC), are involved in sponsoring anti-doping research as well. These research projects are of paramount importance to keep up with emerging doping techniques, such as the administration of new performance-enhancing substances (e.g. designer drugs, products leaving the pharmaceutical pipeline and entering the market) or the use of new methodologies (e.g. gene doping) used by athletes to gain a competitive advantage in sports. Many of these substances find their origins in the field of medicine and anti-doping researchers must be able to rapidly provide answers to new substances and technologies on the market, which may be misused for their ergogenic effects.

The Code of Ethics (Annex A) in the International Standard for Laboratories refers to the Helsinki Declaration as a guiding framework for anti-doping research. The document explicitly states that *"The Laboratories and WADA-Approved Laboratories for the ABP shall follow the Helsinki Accords and any applicable national standards as they relate to the involvement of human subjects in research."* (WADA 2019, 117). The Helsinki Declaration is widely regarded

¹ The Athlete Biological Passport presents the longitudinal profiling of biological variables to detect unnatural fluctuations as the indirect result of doping use.

as a cornerstone document which stipulates the ethical principles for *medical* research involving human subjects, as the title itself suggests. Nevertheless, anti-doping research may be distinct from medical research in multiple aspects, amongst which its purpose, risks and benefits assessment, the definition of vulnerable populations, and pre-trial scientific requirements, are paramount. Accordingly, the applicability of the same ethical principles and guidelines regulating medical research to anti-doping research can be called into question. Against this backdrop, the objective of this article is to analyze to what extent specific provisions within the Helsinki Declaration might not be fully compatible with the objectives and characteristics of anti-doping research, or might be difficult to adhere to.

The paper is structured as follows. In the next section (§2) we go through the general principles of the Helsinki Declaration whose applicability to anti-doping research may be controversial, and we explain to what extent potential frictions between the two may arise. In particular, ethical principles related to four thematic research areas are discussed: the purpose of medical research; risks and benefits of the research practice; vulnerable groups and individuals; and scientific requirements and research protocol. In the discussion section (§3), we indicate possible solutions for addressing the aforementioned difficulties.

2. PRINCIPLES OF HELSINKI DECLARATION AND ANTI-DOPING RESEARCH

2.1 The primary purpose of medical research

“The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.” (Article 6).

Dwelling on this quote, many observers would agree that anti-doping research departs from a different epistemological position than the one described here. The Helsinki Declaration develops a “statement of ethical principles for medical research involving human subjects” (Preamble, article 1), it proposes a framework that is clearly purposed towards the generation of new medical knowledge (see also article 8), and is focused on specific endpoints such as the “safety, effectiveness, efficiency, accessibility, and quality” of a medical procedure or compound. Moreover, the document is “addressed primarily to physicians.” (article 2 of the Preamble).

In contrast, anti-doping research cannot be conceptualized as a research field with the purpose to “understand the causes, development and effects of diseases”. Anti-doping research is mainly focused on the potential performance-enhancing effects or metabolism of specific substances, and the subsequent development of methodologies for their detection. Doping is often referred to as the use of substances or techniques to illegally improve performance. Each year, the WADA publishes the List of Prohibited Substances and Methods (hereafter “Prohibited List” or “List”) which details all categories of substances and methods of which administration or use is currently prohibited. As new substances with ergogenic

effects enter the regular or black market and more information is collected about known substances (e.g. potential masking effect of certain drugs), these may be added to the Prohibited List in the yearly update. Therefore, the meaning of “doping” may change as substances formerly allowed may enter the Prohibited List. For example, the anti-ischemic drug meldonium (trade name: Mildronate) was added to the List after being incorporated in the Monitoring List, which uncovered its widespread abuse by athletes.

The Prohibited List is not exhaustive, meaning that the names of all prohibited substances are not listed. Instead, the List includes appendages such as “including, but not limited to” before a list of specified substances or “and other substances with similar chemical structure or similar biological effect(s)”. Additionally, the non-exclusive S0 class is added to prohibit the use of any pharmacological substance with no approval by any governmental regulatory health authority, such as EMA or FDA, for human therapeutic use (e.g. designer drugs, products with discontinued clinical trials). If applicable for the specific substance or category, the Prohibited List describes which routes of administration can be used, the exceptions to substance groups, the maximal dosages to be used or other relevant information.

Research activities in the field of anti-doping are of paramount importance to keep up with emerging doping techniques. 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 products exiting the pharmaceutical pipeline and entering the (black) market. As doping athletes generally have a “head-start” over researchers, it is in the interest of the anti-doping community to swiftly develop appropriate methods of detection. Anti-doping research 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 cheat with impunity, 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.

The type of data that is processed in anti-doping research could be intuitively considered to be very similar to medical data, and thus be categorized as a sub-type of medical research. Indeed, certain variables are also collected in clinical settings and some abnormal results might be indicative of medical conditions (e.g. data might indicate anemia, iron deficiency or polycythemia vera) (Devriendt et al. 2018). In contrast, anti-doping research may be considered as a field at the intersection of forensic science on the one hand and health sciences on the other. Indeed, insofar as the purpose of anti-doping research is catching athletes who dope, some scientists have clearly positioned anti-doping research as “a forensic science, not a medical one.” (Sottas, Saudan, and Saugy 2008).

2.2 Risk, Burdens and Benefits

A second area of potential friction between medical research and anti-doping research revolves around the issue of risks and benefits. The 2013 version of the Helsinki Declaration devotes a series of articles to this traditional topic of human-subject research. Although most of them are gathered in the Declaration subsection labeled “Risk, Burdens and Benefits” – articles 16, 17 and 18 –, some others are distributed within the first subsection of the Declaration itself (i.e. “General Principles”): article 14 focuses on the issue of risks and benefits, whereas articles 8 and 9 only coincidentally deal with it.

Article 16 may help in introducing this issue:

“In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.” (Article 16).

Here it is specified that risks and burdens are inherently part of the practice of human-subject research and that the mere (potential) presence of risks does not convert a legitimate experimentation into an illegitimate one, provided that some conditions are respected (see articles 17 and 18 – described below in details), and that the “objective” of the research is valuable. Although what the latter exactly means seems somewhat open to interpretation, a partial clarification comes from the first part of article 14, according to which experimenters should engage only in research activities endowed with “potential preventive, diagnostic or therapeutic value” (art. 14).

If article 16 *a priori* foresees that medical research may involve some degrees of risks, article 17 clarifies how to address this issue:

“All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.” (Article 17).

Article 17 states that the experimenter has to commit to a careful assessment of all the potential (and predictable) risks and benefits that may affect the enrolled subjects/groups in the experimentation under investigation, *prior to* the beginning of any research activity. It also specifies that there should be a favorable risk-benefit balance, not necessarily calculated on the same population of enrolled subjects/groups: while risks only refers to subjects enrolled in the experimentation, benefits may also be calculated on the wider populations of subjects/groups not enrolled in the experimentation, as long as they are affected by the same condition of the former.

A similar concept is reported in the first part of article 18:

“Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.” (Article 18)

As just recalled, not only risks have to be assessed, but the experimenter should be also confident that potential risks are manageable. This means that the Helsinki Declaration refers,

though implicitly, to a potential threshold for risks and burdens under which the experimentation becomes ethically impermissible (art. 14):

“Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects”. (Article 14).

However, experimentations that, once started, report a prevalence of risks over benefits should be treated carefully and it is the responsibility of the experimenter to decide how to proceed:

“[...] When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study”. (Article 18).

Drawing from this background analysis, two are the areas of potential friction between what required by the Helsinki Declaration and anti-doping research: the issues of (i) risk assessment and (ii) risk-benefit favorable ratio for the enrolled subjects² respectively.

Firstly, insofar as limited evidence exists with respect to the safety profile of non-approved substances (see Section “Scientific Requirements”), the risk for the research subject becomes very hard to assess. As an example, limited scientific pharmacological and safety information may be available for designer drugs. Therefore, just unrefined/rough assessment is possible, based on structure evaluation, historical evidence of clinical trials, or non-scientific sources such as the description of large-dose effects on non-controlled settings such as bodybuilder fora.

Secondly, as to risk-benefit favorable ratio, complications arise when looking at the already mentioned article 17, which requires to assess the risk-benefit ratio at large, by considering the impact of research not only on the individual research subjects enrolled, but also on the group/category to which research subjects belong. In the case of anti-doping research, there might not be a clear benefit for the research subjects enrolled. Indeed, the group which may directly benefit most from the research – namely, athletes undergoing doping control – cannot be recruited for anti-doping research as this would violate anti-doping laws (see WADC).

2.3 Vulnerable groups and Individuals

Although the current version of the Helsinki Declaration does not provide a definition of vulnerable population, we may draw upon the version of 2008, now rescinded, as it advances a definition of vulnerability that is in line with the one that can be found in mainstream research ethics’ debate (Iltis 2009; Ten Have 2015; Bracken-Roche et al. 2017): “These (*i.e. vulnerable groups*) include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence”. (WHO 2008, article 9). Vulnerability

² In this section we focus on the issue of risks and benefits of anti-doping research, leaving aside the clarification and discussion over the definition and legitimacy of enrolled participants in this kind of research (e.g.: who are the research subjects in anti-doping research and on whom the risk-benefit ratio is calculated). The issue of research participants in anti-doping research is discussed in section 2.3 “Vulnerable groups and individuals”.

is therefore defined in relation to autonomy, and in particular as absent or compromised autonomy. This definition may also be enriched with what stated in article 19 of the current version of the Helsinki Declaration, which identify in the “increased likelihood of being wronged or of incurring additional harm” (WHO 2013, principle 13) some potential negative implications related to being vulnerable.

Although there is a consistent debate, within the scholarly literature, over the utility and potential threats of categorizing individuals/groups as vulnerable (Levine et al. 2004; Hurst 2008; Schroeder and Gefenas 2009), the latest version of the Helsinki Declaration emphasizes the importance of recognizing such categories of individuals/groups, as well as the need to deserve them a special treatment, namely protection:

“Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.” (Article 19).

Translating protection into an operational requirement means, in the Declaration’s view, acknowledging the possibility of enrolling vulnerable individuals/groups in clinical experimentations, provided that the following conditions are all simultaneously respected: i) that the research is responsive to the needs and/or priorities of the vulnerable individuals/groups; ii) that carrying out the research on a different population would be devoid of any epistemic or therapeutic utility; iii) that some benefit in terms of knowledge, practices, and/or interventions for the vulnerable individuals/groups enrolled is expected from the research:

“Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.” (Article 20).

When it comes to the application of article 20 of the Helsinki Declaration to our research context, we immediately see that, in light of the above, different research subjects involved in anti-doping research may be defined as vulnerable. A first vulnerable population in anti-doping research is represented by people who use ergogenic substances for performance or muscle-enhancing purposes, who may be defined as “substance users”. Despite being a very heterogeneous group, in those cases in which we can observe an impact of addiction over autonomy (Gorini et al. 2014), we may argue that substance users are vulnerable individuals as their autonomy may be partially – though not necessarily completely (Foddy and Savulescu 2006; Levy 2016) – impaired.

When considering substance users as potential candidates for anti-doping research, the conditions put forward under article 20 would not seem strictly applicable. Indeed anti-doping research does not respond to the needs and/or priorities of the substance users’ group. Anti-doping research is indented to maintain the integrity of sports competition. However, although not the goal of this research, this may also result in benefitting the health of athletes, by keeping sport competition free from doping substances. Moreover, from a scientific perspective, substance users do not represent the only population that could be interesting

to enroll in anti-doping research as, theoretically, and strictly following this condition, it may be argued that the same substances may be successfully tested also on other populations. Thirdly, it is very unlikely that anti-doping research would result in an actual benefit for substance users, or that results of anti-doping research are useful and disseminated beyond the anti-doping context.

A second vulnerable population in anti-doping research is represented by lab personnel, inasmuch as, according to a recent qualitative study we have conducted, members of this group may be recruited for participation in anti-doping research (Devriendt, Sanchini, and Borry 2020). This owes to the fact that lab personnel are familiar with anti-doping research, and are thus more likely to maintain strict adherence to anti-doping research protocols. In addition, insofar as they already work within anti-doping research labs, lab personnel allow streamlining the recruitment process. However, within the context of anti-doping research, lab personnel may be labeled as a vulnerable population as well, since they are involved in superior-subordinate relationships with laboratory leaders, with the inherent likelihood of experiencing undue influence when enrolled as research subjects (CIOMS 2016, guideline 15, 58). As we have seen above, vulnerability does not preclude, *per se*, participation in research, but requires further caution.

When applying Article 20 to lab personnel, it may be easily recognized that anti-doping research does not address the health needs or priorities of lab personnel, as individual nor as category. Finally, as the justifications for recruiting lab personnel do not lie in their intrinsic characteristics, but are brought forth from their professional role, also the second requirement appears difficult to fulfill.

Actually, the population group towards which anti-doping research is directed to is athletes. Athletes are the ones who may be said to have same advantage from anti-doping research as the latter may allow them to engage in fairer competitions. If we strictly follow article 20 of the Helsinki Declaration, athletes turn out to be the most fitting population to enroll for anti-doping research. However, as we have already seen, this is not an actionable solution as it is in contrast with current anti-doping laws (see WADC).

A possible solution for avoiding the problem of enrolling a vulnerable population would be to recruit paid healthy volunteers, for which considerations of undue influence may as well arise (Macklin 1981; Ackerman 1989, Macklin 1989, Grady 2001; Sears 2001; Ashcroft 2001), or patients, in case of labs associated with a university hospital or university. The key advantage of the latter is that the administration of substances which are registered as medicines or are used off-label may benefit the patients, thus representing also an ethically tenable solution. However, some challenges arise as well, where 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 fully applicable to the athlete population.

2.4 Scientific requirements and research protocols

A last element of potential misalignment between the Helsinki Declaration and anti-doping research concerns the definition of scientific requirements on which to ground human-subject research and the information that should appear in the research protocol.

Article 21 helps clarifying what should count as “scientific requirement”:

“Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.” (Article 21).

Through this article, the Helsinki Declaration unambiguously requires that human experimentation should be based on robust scientific background knowledge, to be obtained through scientific literature and/or pre-clinical testing. However, anti-doping researchers have to refer, in some cases, to medical literature that is outdated. As an example, in those cases where the doping substance is not on the market anymore, but athletes still use it, researchers can be forced to rely on evidence gathered in the past, which is not always available and, at times, also outdated (Devriendt, Sanchini, and Borry 2020). Moreover, the existing evidence to support these studies (e.g. description of effects of high-dose administration of substances on some bodybuilder fora) does not hold the level of scientific evidence that is expected. Finally, the requirement of performing rigorous pre-clinical testing for every non-prohibited substance might function better in theory than in practice, because of limitations in terms of resources (e.g. manpower, financial) for individual laboratories, timeline-related issues of method implementation, and the fact that it may still be impossible to generate reference material after pre-clinical testing (Devriendt et al. 2020).

3. DISCUSSION

Although often neglected, anti-doping research is paramount to maintain the integrity of the doping control system. Through the ISL, WADA requires accredited labs to perform research compliant with the principles of the Helsinki Declaration. However, as we argued, some difficulties exist when trying to strictly apply its principles and recommendations to anti-doping research context. Put differently, anti-doping research and the Helsinki Declaration seem to be in a mismatched relationship.

Potential misalignments do not apply to the anti-doping research field only. Indeed, several scientific fields can struggle to cope with the Helsinki Declaration in their respective domains: sport medicine, forensic medicine, and toxicology can be recalled, amongst others.

Despite having been the subject of intense critical scrutiny (Forster, Emanuel & Grady 2001; Emanuel 2013; Smith and Weinstock 2019), the Helsinki Declaration nevertheless remains to the present day the reference international document on the ethics of research (Ashcroft

2008; Millum, Wendler, and Emanuel 2013; Morris 2013; Parsa-Parsi et al. 2013; Ehni and Wiesing 2019). Therefore, it is paramount to acknowledge the inspirational role of the ethical principles presented in the Helsinki Declaration while, at the same time, identifying some guidelines that, though compliant with the Declaration, may indicate how its principles should be contextualised and operationalized in the anti-doping research context.

A very fruitful example of this envisaged course of action is represented by the appeal to CIOMS Guidelines. Drafted by the Council for International Organisations of Medical Sciences and revised for its fourth time in 2016 in cooperation with the WHO “to ensure that that final draft were in line with the Declaration of Helsinki” (CIOMS 2016, X), CIOMS Guidelines define themselves as “a detailed commentary on how universal ethical principles” – the ones set forth in the Helsinki Declaration – “should be applied” in different human-subject research contexts (CIOMS 2016, viii). In other words, CIOMS Guidelines may be considered as operational guidelines with the task of indicating how general ethical principles should be applied in various contexts of human-subject research (CIOMS 2016, ix), where the latter is interpreted within the Guidelines as a broader category than medical human subject research. Accordingly, CIOMS Guidelines appear more easily applicable to the context of anti-doping research. Guidelines 3, 4, 15 and Appendix 1 may exemplify this point.

Guideline 3, entitled *Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research*, declares that:

“Groups that are unlikely to benefit from any knowledge gained from the research should not bear a disproportionate share of the risks and burdens of research participation”.

This provides researchers with the possibility of enrolling groups which are not necessarily the ones which will eventually benefit from the research outcomes, as in the case of anti-doping research.

Guideline 4, entitled *Potential individual benefits and risks of research*, states that:

“For research interventions or procedures that offer no potential individual benefits to participants, the risks must be minimized and appropriate in relation to the social and scientific value of the knowledge to be gained”.

This enables to overcome the already mentioned shortcuts regarding risk-benefit estimation, as it authorizes the conduction of research trials in which (especially prior) risks’ estimation is difficult, provided that these risks are appropriately managed.

Guideline 15, entitled *Research involving vulnerable persons and groups*, declares that:

“When vulnerable individuals and groups are considered for recruitment in research, researchers and research ethics committees must ensure that specific protections are in place to safeguard the rights and welfare of these individuals and groups in the conduct of the research”.

This formulation provides researchers with the possibility of enrolling vulnerable persons/groups, while also specifying that conditions for additional protections should be put in place, both by the side of researchers and by the side of ethics committees. For example, it claims that in case of “individuals in hierarchical positions” as in the case of lab personnel in

our scenario, “the research protocol must include a description of provisions to protect such individuals from being conscripted into research” (CIOMS 2016, 58). However, as it does not provide detailed provisions of how this protection should be interpreted, it does not lead to the a priori exclusion of subjects that we identified as vulnerable persons in anti-doping research from recruitment.

Finally, Appendix 1, entitled *Items to be included in a protocol, or associated documents, for health-related research involving humans*, article 5 considers pre-clinical evidence also:

“(the) Summary of all previous studies on the topic, including unpublished studies known to the investigators and sponsors, and information on previously published research on the topic, including the nature, extent and relevance of animal studies and other preclinical and clinical studies”.

This broadens the notion of pre-clinical evidence, thus allowing including within this category also the preliminary evidences underlying anti-doping research studies.

If the Helsinki Declaration and CIOMS Guidelines’ marriage, when referred to anti-doping research context, appears appropriate, the already reported sentence within the ISL Code of Ethics may be slightly modified accordingly, so as to include the reference to CIOMS Guidelines. A possible example may be: “[WADA-accredited] laboratories shall follow the Helsinki Declaration, CIOMS Guidelines and any applicable national standards as they relate to the involvement of human subjects in research”. WADA may also decide, in collaboration with WHO and CIOMS, to set up a working group with the specific task of further contextualising relevant CIOMS Guidelines so as to make them compliant with anti-doping research, while also expanding on some issues that are peculiar to anti-doping research (e.g. discussing how to deal with principle of justice; defining what is the social value of anti-doping research). The latter can be particularly relevant if it is considered that, currently, ethical issues specific to anti-doping research have only been marginally explored, with the Ethical Standards in Sport and Exercise Science Research (2017) proposing only limited principles for the conditions of the recruitment of athletes for such research (Harriss, Macsween, and Atkinson 2017). In the same line, WADC states that “the results of anti-doping research should not be misused and applied for doping purposes” (WADC 2005, 101), and that athletes should not be enrolled as research participants (Howman 2013). Other ethical considerations, such as the risk that participants may be incentivized to use prohibited substances after enrolment in a research study (e.g. due to the impression that these products are safe for performance/physique-enhancing purposes), the lack of strong in vitro and in vivo evidence in supports of appropriate safe dose, and the unfair distribution of benefit/risks for the individual to participate in anti-doping research, are still underexplored issues.

4. CONCLUSIONS

Drawing from the WADA requirement, set forth in the ISL and directed towards WADA accredited labs, to perform research compliant with the Helsinki Declaration, this paper aimed to investigate potential challenges in applying principles formulated for *medical* human

subject research to anti-doping research. Four main areas of potential misalignment were identified and discussed: purpose identification, risks and benefits assessment, vulnerable populations definition, and pre-trial scientific requirements. In the Discussion Section, the proposal of recognizing the inspirational role of the Helsinki Declaration while operationalizing its principles relating to CIOMS Guidelines was put forward. It is paramount to draw ever more attention to a research domain that, despite its widely accepted importance for the fight against doping and its relevance within specialised literature, still lacks broader scrutiny across other research domains, particularly in the research ethics field.

ACKNOWLEDGMENTS

NOTHING TO DECLARE AT THIS STAGES.

DECLARATION OF INTEREST STATEMENT

V.S. and T. D. do not have any conflict of interest to declare. P.B. is a member of the WADA Ethics Expert Group, an advisory body to WADA.

This article is the work of our research group at KU Leuven and does not necessarily reflect the vision of the World Anti-Doping Agency or the WADA Ethics Expert Group.

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