

# The South African clinical trial industry: Implications of problems with the issuing of human tissue export permits

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The National Health Act requires a valid permit before human biological tissue samples are exported from South Africa. However, delays in issuing export permits make it difficult for many researchers and pharmaceutical companies to comply. There are misconceptions about who is responsible for obtaining such a permit. Delays have caused many new trials to start without a permit, and biological samples from ongoing trials have been exported using expired permits. This could have detrimental consequences for the South African trial industry, especially with the country's history of vulnerable populations in developing areas. Medicine Control Council inspections have listed findings related to export permits for several trial sites. Researchers must be aware that it remains their responsibility to apply for such a permit. The most important steps to ensure a smoother approval process are for applicants to (i) familiarise themselves with the permit issue process and (ii) recognise the importance of correctly completing and signing application forms.

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The exportation of human tissue from South Africa (SA) is governed by the National Health Act, 2003 (Act 61 of 2003) (NHA),<sup>[1]</sup> which requires clinical trial researchers to obtain an export permit from the SA Ministry of Health before exporting any tissue, including blood, blood products, cultured cells, stem cells, embryos, zygotes and gametes. Researchers and pharmaceutical sponsors battle to comply with this local law: obstacles include unexpected delays in the issuance of permits, incorrect contact information on record, and lack of consensus over which authoritative body is responsible for obtaining the permit from the Department of Health (DoH). Therefore, many new trials have been started without such a permit, while biological samples from ongoing trials have been shipped using expired permits.

The potential implications of this twofold problem (delays and expired permits) are huge and have been compounded by the problem being listed as a finding in recent Medicines Control Council (MCC) inspections for several clinical trial sites.

## Discussion

Research on human subjects in SA is guided by the South African Good Clinical Practice (SA-GCP) guideline, published by the Department of Health in 2000 and revised in 2006.<sup>[2]</sup> This guideline was incorporated into the 2003 NHA, which also legally enforces compliance with the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki.<sup>[2]</sup> The NHA governs all national ethics regulations; legal aspects of using human biological tissue are addressed in Chapter 8, Section 68. Specifically, the import and export of human tissue is described in paragraph 1(g) of Section 68 of the Act.<sup>[1,6]</sup> The NHA, which was partially proclaimed

on 2 May 2005, is still not fully implemented; however, sections of the Act came into effect on 2 March 2012, in terms of Proclamation 11.<sup>[3,4]</sup>

The strict Regulations No. 2 - 9 – relating to the import and export of human tissue, blood, blood products, cultured cells, stem cells, embryos, fetal tissue, zygotes and gametes – are important.<sup>[5]</sup> Anecdotal evidence suggests that human biological tissue and data might be being exported from SA regularly. Without explicit consent for export from the Minister of Health, these tissues and data would be undocumented and unaccounted for at a national level.<sup>[6]</sup>

In 2011, the South African Clinical Research Association (SACRA) conducted an online national public poll,<sup>[7]</sup> which revealed that >50% of the respondents wait for more than 6 months for the approval of an export permit for biological substances; >20% of voters indicated a waiting period of 2 months. Considering that it takes the DoH on average 3 - 7 working days to process new permit applications, these unexpected delays are immensely problematic for clinical researchers. Such delays often force sponsors and researchers into beginning new trials before this permit is in place. Thus SA research institutions violate a national law, which could have serious consequences for the image of the SA clinical trial industry. According to the NHA, exporting human tissues without a valid export permit is a criminal offence punishable by fine and/or imprisonment.

## General misconceptions

MCC inspections conducted at several clinical trial sites in SA found that expired permits were being used to ship blood samples in ongoing trials. This emphasised that researchers and sponsors harbour misconceptions about these permits. It is often not clear who is responsible for applying for such a permit and/or for renewal

of an existing permit. The misconception also exists that, as for investigational products entering the country, couriers cannot export biological samples through health ports without possessing a hard copy of the valid permit. Another pitfall is the lack of proper training of research staff regarding the use of export permits and the importance of having timely and correctly completed permit application forms.

The institution/organisation exporting the biological samples directly overseas is responsible for obtaining the export permit. For example, if an investigator sends samples to a local laboratory for analysis, and the laboratory then exports the samples, the responsibility for the permit application resides with the laboratory. It does not reside with the investigator or the sponsor/contract research organisation (CRO), even if the sponsor requested that the samples be exported. Where samples are exported directly from a clinical trial site, the investigator is then responsible for the permit. The same applies for permit renewals for ongoing trials.

For the shipment to be authorised by the health ports, a physical copy of the valid export permit must be attached. Although the Human Tissue Act, No. 65<sup>[8]</sup> has been in force since 1983, it was only recently discovered that the health ports were not enforcing it, thereby allowing shipments to be exported without a valid permit.

### End-of-year rush creates backlog

Correctly completed permit application forms are processed and authorised by the DoH. First, the application form is received by the administration officer and processed. It is then submitted to the acting director for checking and verification, and to the cluster manager for signature. Once signed, the permit is faxed to the applicant. The DoH keeps a copy of the permit on record and the original permit is posted to the applicant's physical address.

Between 70 - 200 export permit applications are processed daily by the DoH. However, discussions between the DoH and the industry, via SACRA, have indicated that during the last 3 months of the year requests increase for new permits and permit renewals. This creates a backlog. Incomplete, incorrect and/or unsigned application forms further obstruct the process.

### Facilitating the process

SACRA and TNT Couriers, in collaboration with the input and support of the DoH's export/import section, have provided an information booklet, *Biological Substances Export/Import Permits*. The booklet is published on the TNT website and can be downloaded free of charge in PDF format.<sup>[9]</sup> It provides detailed information for clinical researchers and sponsors in the form of answers to frequently asked questions about the application/renewal process, contact information for the export/import section of the DoH, and other useful information.

Several steps can be taken to alleviate the DoH's backlog and ensure a less frustrating application process for all parties. First, it is advisable to spread the applications throughout the year instead of piling all application forms together at the end of the year. Second, applicants must familiarise themselves with the contents of the information booklet,<sup>[9]</sup> which includes an example of a correctly completed export-permit application form. Attention should be paid to the different areas on the form and how to complete each section. The signature of the applicant is most important and must be provided by the applicant only. No electronic signatures are allowed. Applicants must also ensure that they are indeed authorised to act

as an applicant on behalf of the research institution/organisation. Within an institution, laboratory managers, quality control managers and doctors (investigators) are usually authorised and are therefore responsible for applications.<sup>[9]</sup> Trial co-ordinators and administrative assistants can help investigators complete the forms, but it remains the applicant's responsibility to ensure that the information is correct and complete and that the form is signed.

Third, research institutions/organisations must ensure that they have the correct contact information for the DoH, to be able to follow up with the approval process. It is advisable that research institutions contact SACRA regularly to confirm if any changes have been made to the department's export/import permit requirements. Note that changes have been implemented since the publication of the SACRA/TNT booklet.

According to the ICH-GCP, researchers and pharmaceutical sponsors must abide by the laws of the country and other applicable local and international guidelines when conducting their research. It is imperative that researchers at clinical trial institutions/organisations be informed about problems and consequences associated with using expired or delayed permits, the processes of permit applications and the importance of ensuring that applications for new permits or renewals are made well in advance to prevent delays. Negative findings in an inspection, even when listed as minor, are undesirable for any investigator, sponsor/CRO or trial site, hence the importance of making other researchers aware of these critically important aspects through public conferences, published articles and discussion forums with leading and representative organisations and committees in the industry, etc.

### Conclusion

Long delays in issuing and renewing export permits for SA trials make it difficult for researchers and sponsors to abide by the local NHA, and other guidelines incorporated into the Act. The industry and the DoH have identified the main reason for the delays as the backlog created when most applications are sent in the last 3 months of the year. A smoother approval process can be ensured if (i) applications are distributed evenly throughout the year; (ii) applicants familiarising themselves with the approval process, which will also clarify misconceptions on the responsibility of the various role players; and (iii) application forms being completed and signed correctly. Lastly, clinical trial sites have shown willingness to publicly share inspection findings with other researchers and sites of critical aspects that could influence the regulatory and legal aspects of a trial. This is an effective step to ensure continued education and a positive image of the ethical and legitimate conduct of clinical research in South Africa.

- For more information visit the SACRA website at <http://www.sacraza.com>.

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