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Motivations, barriers and experiences of participants in an HIV reservoir trial

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ABSTRACT

Objectives: We aimed to investigate the motives, barriers and experiences of HIV-STAR study participants. The HIV-STAR study was an analytical HIV treatment interruption trial (ATI) aiming to evaluate the origin of viral rebound, conducted in Ghent, Belgium.

Methods: A mixed-method study was performed among 11 participants of the HIV-STAR study. Two self-administered questionnaires with 32 and 23 items, respectively, assessed motives, barriers and experiences of the research participants. In-depth interviews were conducted to further explore and understand topics that had emerged from these surveys.

Results: Motives of ATI study participants were primarily related to the improvement of their own health perspectives and to their contribution to find an HIV cure. Barriers for ATI participation mostly related to practical issues, such as difficulty in planning study visits. Ten out of 11 participants reported a very high overall satisfaction and were willing to participate in another ATI. This satisfaction was predominantly linked to clear communication and guidance. Invasive sampling during the ATI was less of a burden than anticipated by participants. However, most participants underestimated the emotional impact of HIV treatment interruption, which was associated with feelings of uncertainty and loss of control. Risk of HIV transmission because of viral rebound was also mentioned as burdensome during this phase.

Conclusions: Involvement in an ATI was positively evaluated by HIV-STAR participants. Contributing to HIV cure research outweighed the burden of study participation for most participants. The latter aspects were attenuated by mutual decision making and the experience of empathy from the research team. Still, issues regarding privacy and the psychosocial impact of treatment interruption, including sexuality and HIV transmissibility, should be addressed in a better way.

Introduction

Analytical treatment interruption trials (ATI) are of substantial importance to HIV cure research. The lack of a specific biomarker of HIV infection render ATI trials necessary to evaluate the efficacy of HIV cure interventions and the effect of novel drugs/compounds on stable HIV remission/cure, such as new latency reversing agents (LRAs).[1] ATI trials provide critical information about time to viral rebound and in combination with extensive patient sampling provide broader insights regarding the origin of this rebound. In addition, they can accelerate the identification of potential biomarkers to predict viral rebound after treatment interruption.[2,3]

The risk of HIV reservoir expansion due to ATI was reported to be minimal in blood and brain, indicating that such trials are safe in terms of

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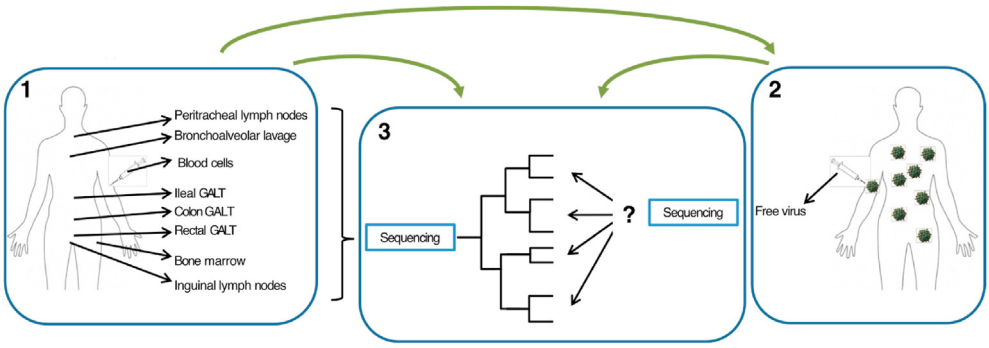


Fig. 1. Schematic overview of the study set-up. 1) Extensive sampling under cART. 2) Treatment interruption phase with monitoring up to viral rebound. 3) Analysis of viral sequences isolated from samples from the 1st and 2nd study phase to determine the origin of viral rebound.

HIV disease progression.[3–5] Nevertheless, the emotional and burdensome impact of participation in ATI trials needs to be considered. Most ATIs involve extensive and invasive sampling, potentially including lymph node excisions, lumbar punctures and leukapheresis as well as frequent study visits. Moreover, viral rebound during treatment interruption may result in increased infectiousness.[6,7] These issues represent potential barriers to study participation in some PLHIV, and may render study participation stressful and burdensome.

Contribution to the improvement of treatment options constitute the scientific and societal interest of ATI but it should be weighed out against the potential harm and burden to study participants.

Although previous research has shown high acceptance of HIV cure research in people living with HIV (PLHIV),[8–10] there are to date only limited reports regarding the experience of participants in such trials.

To gain more insight in the potential burden of ATIs and to explore to which extent the reality of their trial participation met their expectations, we conducted a mixed-method study among participants of the HIV-STAR study, an ATI conducted in Ghent, Belgium. In this sub-study, we explored motives, barriers, expectations and experiences of study participants by using two questionnaire surveys and subsequently performed in-depth interviews for clarifications. Based on our findings, we propose a checklist that can be used to guide future clinical trials.

Methods

Study population and procedures of the HIV-STAR study

The HIV-STAR study (NCT02641756) was initiated in 2015. Extensive tissue sampling of HIV- infected patients was performed both on combination antiretroviral therapy (cART) as well as during structured cART interruption in order to investigate the origin of viral rebound. Eligibility criteria included the following: (i)HIV-seropositivity without a history of AIDS defining conditions, (ii)CD4 T-cell count above 500/μl, (iii) an undetectable plasma viral load (<20 copies/ml) during the last 2 years, without any blips observed in the last 6 months and (iiii) on an ART regimen containing an integrase inhibitor for at least 3 months at the first sampling. PLHIV who met these inclusion criteria were recruited during routine HIV outpatient consultations at the HIV Reference Center in Ghent. Prior to study enrollment, participants received extensive information about the study procedures during two visits with a study physician, who was different from the treating physician. The mean time between the first pre-enrollment visit and study enrollment was 3 months. An independent senior staff physician and a psychologist were available for consult upon request of either the study physician or the potential study participant. If this independent assessment revealed psychological vulnerability, incompatible with study participation, this was reported as screen failure. Prior to inclusion in the study, participants were informed about the potential risks of sampling and of treatment interruption as well as about the lack of personal benefit.

Fig. 1 gives a schematic overview of the of two phases of the HIV STAR study. During the first phase, participants were extensively sampled while on cART. After approximately three months, participants were scheduled for the second part of the study. During this second phase, participants were instructed to stop cART. Viral parameters were monitored 2–3 times per week until the occurrence of viral rebound. Participants were instructed to restart cART immediately after collection of the final study sample upon viral rebound. The final study visit was conducted three months after the patient's viral load had dropped again to an undetectable level.

Data collection

For this sub-study, we assessed motives, barriers, expectations and experiences of participants in the HIV-STAR study. First, all subjects self-completed a questionnaire including 32 items on motives, barriers and expectations of study participation at enrollment ("*baseline questionnaire*"). A second survey was conducted during the final study visit and consisted of 23 items to assess motives and investigate the overall satisfaction and experiences of study participation ("*exit questionnaire*"). Questionnaire items were based on previous literature[12] and comments of the local medical ethical committee of Ghent University Hospital. In the context of external validity, these surveys were reviewed by an independent psychologist with experience in HIV care. The ATI took place between June 2016 and July 2017 and all participants completed the questionnaires immediately before and after study participation. Both questionnaires and responses are listed in Supplement 1.

In August 2018, 1–2 years after the ATI, we conducted semi-structured in-depth interviews (IDI) to gain more insight in issues that had emerged from the questionnaires. For this, all HIV-STAR study participants were invited for a face-to-face interview. The IDIs lasted approximately 30–60 min and were conducted in Dutch by a single external physician who was not further involved in the study execution or the follow-up of participants (WvB). All IDIs were audio-recorded and transcribed verbatim. Motives and barriers for study participation were explored, as well as positive and negative experiences of each study phase. The interview guide can be found in Supplement 2.

The statistical computer program IBM SPSS Statistics for Windows (IBM Corp, Armonck, NY, USA) was used for quantitative data analysis. Tables were extracted in Microsoft excel. The scale was 1->5 or 1->4, the highest scores indicating full agreement with the statement.

Qualitative data analysis was performed by three researchers (MDS, WvB, UD). MaxQDA version 12.0 was used for qualitative data analysis using coding and content analysis.[13] All transcripts were coded using an open-coding process by two independent coders (MDS, WvB). Variability in coding was discussed until reaching consensus between coders. Crystallization of similar codes was eventually performed to generate one list of codes with an unambiguous definition, as agreed by all researchers. These codes were then categorized into themes reflecting motives,

Table 1
Relevant demographics of the HIV-infected study participants.

Subject-ID	Race	Gender	Age	CD4 nadir (cells/μl)	Viral load zenith (log10 HIV-1 c/m)	Time since primo infection (y)	Time on cART (y)	Time to viral rebound (days)
STAR2	White	M	38	438	5,08	NA	4	36
STAR3	White	M	52	331	5,53	3	3	28
STAR4	White	M	36	142	4,31	NA	11	20
STAR5	White	M	39	308	4,77	3	3	15
STAR6	White	M	41	378	4,82	4	3	19
STAR7	White	M	40	421	4,8	11	3	21
STAR8	White	M	40	400	4,64	11	8	21
STAR9	White	M	32	405	5,01	9	6	21
STAR10	White	M	54	327	5,49	20	11	21
STAR11	White	M	37	432	3,62	9	2	28
STAR12	White	F	56	348	3,23	7	6	25

barriers, expectations and experiences of the participation in HIV-STAR study.

Ethical approval

This study was approved by the local medical ethical committee of the University Hospital of Ghent (Belgian registration number: B670201525474). Participation was voluntary and every participant provided a written informed consent prior to study enrollment. Participants received €1000 as a compensation for the time spent in the hospital and travel expenses. No additional incentive was given for participation in the in-depth interview.

Results

The HIV-STAR study population consisted of one female and ten male participants. Their median age was 40 years (range of 32–56 years). Relevant demographics are listed in Table 1. All eleven participants completed both the baseline and exit questionnaires. Of these eleven participants, nine were interviewed. The two left participants (STAR 4–11) were not able to schedule the interview because of other commitments but had indicated willingness to participate to the interviews.

Motives for study participation

In the baseline questionnaire, it became clear that gaining more insight into their own health proved to be an important motive for HIV-STAR study participants. Five participants reported that they hoped that their involvement would improve their own health, and four participants believed that study participation would substantially contribute to the likelihood of future individual HIV cure. Three participants thought that study participation would result in receiving more medical help for HIV or other health issues, and three participants supposed that they would be prioritized if new treatment options would become available. One participant felt that study participation would allow him to stop taking antiretroviral therapy, thus resulting in a functional cure. In total, three participants felt that study participation would turn them into a better person. All participants agreed that study participation would help other patients. In the exit questionnaire, nine participants reported that scientific progress and contribution in achieving new knowledge was an important motive for study participation. All participants were eager to receive the study results. This was also a motivation to participate in future trials. All but one participant expressed interest in future projects and HIV cure research. Ten participants would reengage in similar projects.

The subsequent interviews provided additional, more altruistic, motives for study participation. Most participants mentioned appreciating the care received after the diagnosis of HIV. They viewed participation in a scientific study as a way to show their appreciation towards their health care professionals. Some participants felt themselves a burden to society, as their health care was perceived to be very expensive. They considered participation in the HIV-STAR study as a return service to society. Another interesting line of thought, emerging from the interviews, was the consideration that individual sacrifices are required in order to move science forward.

> *"I am a huge cost for society, this is the least I can do."*

> *"If no one participates in these things, we will never book progress in research."*

One participant mentioned seeking a better relationship with his health care provider as his motive for participation. He hoped that he would be prioritized once a cure became available. For the single woman included in the study, her main motive to participate was women representation in HIV research.

For none of the participants had the financial incentive provided, emerged as a principal motive for study participation. Most participants agreed that the amount of financial compensation provided was sufficient. Still, one participant indicated that participation to future trials would depend on a higher incentive fee.

Barriers for study participation and continuation

At first, time was one of the major barriers for study participation. Indeed, the baseline questionnaire revealed that the majority of participants (7/11) thought that study participation would be too time-consuming. Second, seven participants experienced nervousness about the invasive nature of the tissue sampling. None of the participants worried about the psychological and/or emotional impact of the antiretroviral treatment interruption, and no one reported fear for the emergence of drug-resistance virus. Still, three participants expected the study to have an important impact on their relationship and/or social life. Nine participants mentioned that they did not have the intention to reveal study participation to their relatives or close friends. In this context, four of them also expected a negative reaction. Nevertheless, all participants having a relationship at the time of the study, shared their study participation with their partners.

At the time of the interviews, it became clear that main hesitations towards study participation consisted of concerns about personal availability, fear regarding the invasive nature of the investigations, harm of privacy and dealing with an unknown research team. In terms of privacy, some participants stated they were afraid to (potentially) get in contact with other study participants. They did not want their HIV status to be disclosed to people other than health care providers. The provision of adequate information and good guidance by the research team were mentioned as factors that helped them overcome potential barriers. Finally, a high level of trust in the research team was reported.

> *"Knowing the virus is coming back, you have faith and you put your faith in the study team, and you hope or trust that stopping the medication will not hurt you."*

General experiences of study participation

In the exit questionnaire, ten out of 11 participants were very satisfied about their involvement in the study. These ten participants were also willing to participate in future similar trials and felt that their expectations prior to study participation were met by the actual experience. Eight participants reported satisfaction with the overall study organization, and ten participants did not encounter difficulties planning the study visits. All participants found that their privacy was respected during the study.

Only one participant reported an overall low satisfaction with study participation. In particular, he pointed out negative experiences with the study organization, information provided and guidance during the study. He had no interest in participating in future trials. Despite this overall negative experience, this participant did not report any physical or emotional consequences.

During the interviews, the overall high satisfaction of study participants was primarily linked to positive experiences with the research team. Specifically, the flexibility and accessibility of the research team were highlighted. Participants highly valued the personal approach, making them feel comfortable and secure. One of the participants recalled a negative experience with a study nurse, when she accidentally identified two other study participants. Concerning the logistics, participants felt that the study visits were time consuming, and indicated that the hospital administration was not efficient and was prone to improvement.

"It [the approach of the research team] provided a sense of security, efficiency and not being impersonal, and for me this was very important."

Moreover, participants provided insight into the support they received from their personal environment during the interviews. Most participants indicated that they kept their study participation private (n = 6). Among those who disclosed their study participation to relatives, some reported a supportive attitude from close family or friends, while others experienced skeptic reactions from relatives about the potential impact and safety of the study.

Impact of invasive investigations

While seven participants anticipated the sampling investigations as a burden in the baseline questionnaire, only two reported actual experience of burden in the exit questionnaire. Ten participants indicated the information received prior to the study being in line with their actual experience. For most, fear prior to the investigations proved worse than the actual physical burden, such as pain or discomfort.

During the interviews, the most frequently reported negative physical experience was discomfort when lying still during the leukapheresis (n = 3), followed by a painful wound after inguinal lymph node excision (n = 2) and headache following lumbar puncture (n = 1). These complications, although limited, were identified as the reason for a higher impact of the interventions than the one initially expected.

Impact of antiretroviral treatment interruption and continuation

In the baseline questionnaire, ten participants agreed with the statement that stopping HIV treatment could potentially result in HIV transmission to sex partners. In the exit questionnaire, eight of these participants reported not to have engaged in unprotected sexual activity when off HIV treatment. In the same questionnaire, five participants described the treatment interruption in the following words: alienating, strange, burdensome and stressful. Preoccupation about becoming detectable again was pointed out by three participants.

During the interviews, two participants mentioned that they had to change their HIV medication to an integrase inhibitor containing regimen prior to study participation. For one participant this resulted in significant side effects, to such extent, that he needed to reveal his participation and HIV status to his boss because of the impact on his work. This incident was perceived as very burdensome and affected his quality of life.

Overall, most participants experienced the treatment interruption phase as the most challenging part of the study. Especially the period of post-ATI intense follow-up with frequent hospital visits and the feeling of uncertainty about how long it would take before their viral load would rebound rendered this period intense. One participant felt that becoming detectable again represented a personal confrontation with the reality of being HIV positive.

"Still now, whenever I come here, to the clinic, I am confronted with the reality of the infection."

In addition, the interviews revealed that study participation led to changes in sexual behavior in order to prevent onward transmission of HIV. One participant changed his relationship from open to closed. Some participants who normally did not (always) use a condom during sex, started using condoms, and others mentioned that they rejected sex or had less sex during treatment interruption. One participant reported a decrease in libido. Most participants did not experience these changes as burdensome, as they found comfort in the information that this would only be temporary. Participants who did not change their sexual behavior indicated that their sex partners were already HIV positive (n = 2) or that the sex partner did not want to use condoms despite being informed about the risk of transmission (n = 1). All participants acknowledged the importance of counseling and the provision of information about sexual intercourse in the context of study participation and/or treatment interruption.

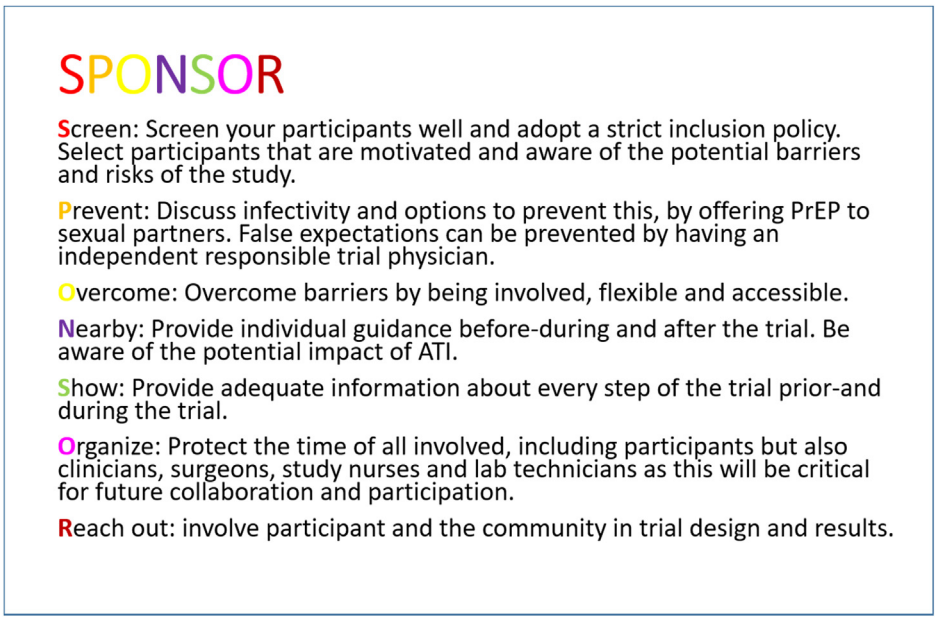
Negative self-perceptions associated with becoming detectable again were also mentioned during the interviews. They pointed out an awareness of feeling in control of the virus when on treatment. This resulted in negative thoughts and feelings about treatment interruption. It was described as if their body was not fighting the virus anymore, as if they let the virus take over. One participant described it as feeling 'dirty'.

"For the first time in 10 years I am not fighting the virus anymore and I allow the virus to fight me again."

Discussion

This study reports the motives, barriers and experiences of participants in a monocentric ATI trial in Ghent, Belgium. Helping to find a cure for HIV proved to be one of the main motives prior to participation, resulting in not only individual, but also societal benefits. Almost half of the participants hoped that study participation would benefit their personal health and would substantially improve their own likelihood of achieving an HIV cure. After having completed the study, the exit questionnaire revealed feeling of scientific progress and contribution in achieving new knowledge as the most important motives for study participation. In line with previous research,[8–10] these findings demonstrate that HIV cure is high on the agenda for PLHIV, despite increased accessibility and tolerance of cART regimens, Undetectable = Untransmittable campaigns and the availability of pre-exposure prophylaxis (PrEP).

We conducted a stringent selection of potential candidates, based not only on virological and immunological criteria, but also on the psychological vulnerability of participants. The latter was assessed by an independent senior physician and/or a psychologist if judged necessary by the study team. Potential candidates were not included in this study protocol if this independent assessment revealed psychological vulnerability, incompatible with study participation. Still, we were surprised by the number of participants that were driven by the motivation of potentially getting cured and/or improving their own health, even after being well informed that this was not a cure trial and that there was no



personal benefit to be expected. Despite these presumably alarming answers, all participants remained in care and on treatment after the trial without adherence issues. However, we want to emphasize the importance of the informed consent, of autonomy and of the substantial risk for therapeutic misconceptions, as crucial features in conducting this type of trials and of trials in general. Especially, we believe that providing regular information to participants during the trial prevents misconceptions or unrealistic expectations.

Interestingly, our results show that altruism - supporting a pathway towards cure - is a key motivator in order to participate in these trials, as observed in previous studies.[11,14,15] Some of these reports highlight that while treated HIV-infection is considered to be a low burden disease by health professionals, some PLHIV still experience their health status as vulnerable.[14] For instance, among Dutch HIV-positive men having sex with men (MSM), one-third perceives living with HIV as burdensome, and 82% would be relieved if a cure existed.[16] Considering these motivational pathways, both individual and societal, a recent publication of Julg et al.[20] stresses the importance of including various stakeholders and active community contributors in the process of trial development. These panels should guarantee a strong scientific rationale in order to support any intervention (e.g., ATI), as well as maximize research progress and minimize both health and non-health related risk for participants.

Initial barriers for study participation included concerns about the time-consuming character of the study, given that some participants feared that it would temporarily impact their work or social life. Adequate time management, clear communication and flexibility of the research team were mentioned to have contributed to overcome this barrier. For instance, home venipunctures through his general practitioner were arranged for one participant. Unfortunately, some other concerns could not be addressed, such as the compulsory but time-consuming hospital administration procedure prior to every study visit. Another barrier for study participation was the concern about privacy and anonymity. Revealing study participation would also reveal one's HIV status, and most participants had never disclosed their status. In the set-up of ATIs this needs to be acknowledged and discussed with potential participants, and additional effort should be made to guarantee anonymity.

In line with a previous report, the overall satisfaction rate of our study population was high.[12] All but one had realistic expectations of study burden, outcome and benefits, resulting in a high proportion of participants that would re-engage in future trials. Only one participant reported a negative experience of his participation. Interestingly, the main motive for study participation in this case was to gain a better relationship with the health care provider, perceived to facilitate future medical prioritization. Such inappropriate expectations need to be addressed prior to study enrollment in order to avoid future disappointment in these participants. Therefore, we recommend engaging an independent study physician, not directly involved in the individual patient care, in such trials.

Another important point is the treatment interruption phase, as discussed in several reports debating the ethics of cure research.[11,17] Noteworthy, this aspect was underestimated the most by participants in our study at baseline, in terms of its negative emotional and psychological impact. We, therefore, suggest that potential feelings of uncertainty and loss of control due to treatment interruption should be discussed prior to trial initiation. Furthermore, emphasis should be put on the aspects of infectiousness and risk of onward HIV transmission during treatment interruption. Most participants changed their sexual behavior in a way to reduce the risk of sexual transmission. Future trials should propose the use of PrEP for partners of participants in ATIs. At the time of our trial, PrEP was not yet available in Belgium.

In our study, participants did not experience a high burden from the intensive and invasive sampling phase, although many expected this phase to be the most challenging. Several potential and eligible candidates for our trial were not enrolled, as they refused to undergo these investigations. Conveying the view of previous trial participants that such issues were eventually experienced as much less burdensome than expected (e.g., by way of testimonials) might increase participation willingness in future trials. To cope with this anxiety, we chose to perform all invasive investigations under general anesthesia at one time point in our trial. This was positively evaluated by the participants.

We wish to acknowledge the limitations of the study. Although small numbers of participants are a characteristic feature of treatment-interruption & cure trials, this limits the relevance of statistical analyses. Therefore, our quantitative analysis could not take into account socio-demographic aspects that might have influenced the responses. Further, our sample was predominantly indigenous and almost exclusively concerned MSM, hampering generalization of our findings to other social-demographic contexts. Finally, we only included in the evaluation PLHIV who participated in the trial, making their responses subject to potential bias in comparison to those having refused to participate or those that were held back after psychological evaluation.

Conclusions

In spite of potential barriers and negative experiences of ATIs, cure research seems of high importance to PLHIV. The vast number of participants willing to participate in future cure trials implies that contributing to finding a cure for HIV outweighs the burden of study participation. Based on our results, future trials should incorporate a strict inclusion policy, shared decision making and an involved research team to meet the personal needs of participants. Issues regarding privacy and the psychosocial impact of treatment interruption, including sexuality and HIV transmissibility, should be addressed specifically. PrEP should be offered to seronegative sexual partners of trial participants. Based on our findings, we propose the following checklist to guide future similar clinical trials, abbreviated as the acronym SPONSOR.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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