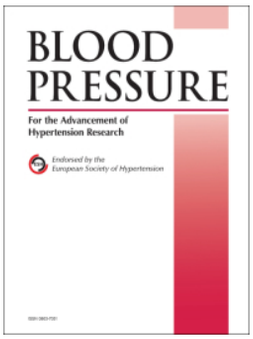

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LETTER TO THE EDITOR

Lessons learned from conducting a randomized controlled trial to improve non-adherence to antihypertensive drug treatment

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ABSTRACT

Purpose: Hypertension significantly contributes to cardiovascular diseases and premature deaths. Effective treatment is crucial to reduce cardiovascular risks, but poor adherence to antihypertensive drugs is a major issue. Numerous studies attempted to investigate interventions for identifying non-adherence, but often failed to address the issue effectively. The RHYME-RCT trial sought to bridge this gap by measuring non-adherence by determining antihypertensive drug concentrations in blood through a dried blood spot (DBS) method in patients with resistant hypertension. This measurement was followed by personalized feedback to improve adherence. During the course of this trial several challenges emerged, including selection bias, the gatekeeper role of physicians, the Hawthorne effect and the role of randomization.

Aim: This communication aims to inform fellow researchers and clinicians of challenges that can arise when conducting clinical trials to improve adherence and offer insights for refining study designs to avoid these issues in forthcoming adherence studies.

PLAIN LANGUAGE SUMMARY

Purpose: High blood pressure is a serious problem that can lead to heart and kidney problems and early deaths. Treating high blood pressure is therefore crucial. Initially, lifestyle changes are recommended, but if they don't work, medications are needed. However, taking these drugs daily can be challenging, and many patients miss doses which is called non-adherence. Despite numerous studies, a perfect solution hasn't been found to solve non-adherence to blood pressure lowering drugs.

In the RHYME-RCT study, researchers aimed to improve drug adherence in patients with resistant hypertension. They monitored drug intake by measuring drug concentrations in the blood alongside 24-hour blood pressure monitoring. These data allowed healthcare providers to offer personalized advice to patients. The study encountered some important challenges in its design, including selection bias, where some participants shouldn't have been included or excluded in the study, and the Hawthorne effect, where patients changed their behavior because they knew they were being observed.

Aim: This message is to inform fellow scientists and doctors about issues that can arise when conducting clinical trials to improve adherence and to encourage the exchange of ideas between scientists to improve future studies on medication adherence, which is essential for managing conditions like high blood pressure.

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KEYWORDS
Hypertension; Adherence; trial; Hawthorne effect; antihypertensive drugs

Hypertension is a major contributor to cardiovascular diseases which often result in premature deaths. To diminish the risk of cardiovascular diseases, optimal treatment of hypertension is essential. A considerable issue leading to suboptimal treatment is non-adherence to antihypertensive drugs. Therefore, improvement of adherence is imperative, but hampered by poor identification of non-adherence as physicians and patients often overestimate adherence.[1] Accurate identification methods like drug measurements in body fluids and directly observed intake have been found to be reliable alternatives to objectively identify non-adherence.[2] To the best of our knowledge no research has been published, that combined measurement of antihypertensive drugs in blood to detect non-adherence with an intervention to improve adherence. Therefore, we conducted a randomized controlled single-blinded trial called RHYME-RCT (Resistant Hypertension: Measure to ReaCh Targets, ICTRP: NTR6914).[3,4] In this study, patients were included based on the definition of

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resistant hypertension, without taking the estimations of physicians towards adherence into account. A dried blood spot (DBS) sampling method was used to measure antihypertensive drug levels in blood to identify non-adherence. Subsequently, a personalized feedback conversation at the outpatient clinic was provided using a theory-based, yet practical communication tool to address different reasons for non-adherence.[5] During the RHYME-RCT trial we were confronted with several challenges due to the study design and research topic, that are important to share with other researchers and clinicians focusing on treatment options for resistant hypertension.

The first challenge we encountered when conducting our trial was selection bias, which is difficult to avoid due to the design of the trial.[6] Patients needed to be sufficiently informed by a patient information leaflet (PIL) in order to give written informed consent. To reduce withdrawal of patients, our PIL focused on the use of drug levels to improve blood pressure (BP) control and words like "drug adherence" were avoided. Unfortunately, this did not prevent withdrawal of patients after reading the PIL. In the hospital with the highest inclusion rate for RHYME-RCT, 40 out of 105 (38%) of the patients did not agree to participate in the trial after reading the PIL (Table 1).[4] In contrast, patients agreeing to participate were very willing to improve their BP (Table 1) and therefore considered more likely to be adherent.

Selection bias in adherence research can partially be prevented by asking general informed consents to use clinical measurements for future research questions to all patients that enter the outpatient clinic for the first time. However, inclusion of participants is a major challenge in studies and other factors may contribute to the decision to participate.

Another interesting challenge was the limited dedication of physicians to introduce the study to patients. From the eligible patients screened by the researcher, only 25% were asked by their physicians to enroll in the trial due to various reasons (Table 1). This low percentage revealed the existence of a gatekeeper function of physicians in the recruitment of patients.[7] Although this phenomenon occurs in clinical studies, we think that the gatekeeper function in adherence research is even more substantial as compared to other topics. We suggest that underlying the gatekeeper function is the fear of physicians to jeopardize the patient-physician relationship by discussing non-adherence as possible cause of resistant hypertension as they might feel they blame the patient. Not only physicians but also patients are responsible for this so-called conspiracy of silence to not discuss medication intake.

The last challenge in behavioral trials like RHYME-RCT is related to the so-called Hawthorne effect which results in better intake of medication at time of a visit.[8] All eligible patients who wanted to participate, first underwent a 24-hour ambulatory BP measurement to confirm true resistant hypertension with a daytime BP >135/85 mmHg after which they were either excluded or randomized to a control or intervention arm. However, following inclusion, BP was much lower for a lot of patients than we expected. In 43% of the patients daytime BP was below the cut-off of resistant hypertension even though they had uncontrolled BP for years. Therefore, adherence and BP control seems to improve just by giving personal attention as provided by participating in a trial. We also investigated this phenomenon in a prospective study called RHYME-AD.[9] In this study we determined adherence by means of measuring antihypertensive drug concentrations in a random blood sample within a year after informed consent was signed. The proportion of non-adherent patients in RHYME-AD with resistant hypertension was 10% higher as compared to the randomized patients in the RHYME-RCT trial, suggesting the influence of the Hawthorne effect.

Table 1. Reasons of patients to (not) participate in RHYME-RCT trial to improve adherence to antihypertensive drugs and reasons of physicians to not introduce the trial to eligible patients.

	Reasons for not wanting to participate in adherence trial (n = 26)	Reasons for participation in adherence trial (n = 16)	Reasons physicians for not introducing study to eligible patients
1	Number of visits is too high (n = 8)	To improve own blood pressure control (n = 7)	First other possible causes of hypertension had to be excluded
2	Problems with traveling to hospital (n = 3)	To add information to the hypertension field to improve treatment in the future (n = 7)	Blood pressure was found to be ok for specific patient or patient had stable (high) blood pressure.
3	Research visits cannot be combined with work or private schedule (n = 2)	Because the physician asked to participate in the research (n = 2)	Language barriers or limited understanding
4	Patient is ok with the blood pressure and doesn't want to improve it any more (n = 2)		Other problems that need more attention compared to participating in a trial to improve adherence
5	Afraid to visit hospital due to corona virus (n = 2)		Limited mobility of patient
6	Doesn't want to undergo a 24-h ABPM (n = 2)		
7	Afraid that the research will effect kidney function (n = 1)		

In addition to the Hawthorn effect, behavioral intervention studies often pose challenges for a randomized study design. By randomizing patients within a study center, there is a risk of contamination.[10] The treating physician is forced to perform the intervention as well as standard-of-care. As all participating physicians were trained to perform the intervention in the RHYME-RCT trial, it is likely they also applied some of this knowledge to the patients randomized to standard-of-care. The difference between the intervention and standard-of-care arm could potentially be influenced by this. The alternative is to use a cluster randomized design: one center performs the intervention and another center treats patients with standard-of-care. This alternative has also some pitfalls, because of an increased heterogeneity including a difference in patient populations between centers and variations in what is considered standard-of-care at each center.

In conclusion, investigating the efficacy of an intervention to improve adherence in a research setting is difficult, having to deal with selection bias, gatekeeper function of participating health care providers and improvement of therapy due to the Hawthorne effect.

We recommend to consider all pros and cons of a certain research design before starting an adherence trial and the involvement of behavioral scientists to come up with the most suitable study design. For these kind of studies, a randomized controlled trial might not be the optimal design and other design should be considered. However, every design will have its own drawbacks and the most optimal study design for adherence research has yet to be established, but is likely to be a mix of different designs.

Conflict of interest

L.E.J. Peeters received lecture fees from Astellas pharma in 2021. T. van Gelder has received lecture fees and study grants from Chiesi and Astellas, in addition to consulting fees from Roche Diagnostics, Thermo Fisher, Vitaeris, CSL Behring, Astellas and Aurinia Pharma. In the last 3 years L. van Dijk has received research grants from Teva and Biogen for studies not related to this one. The other authors declare no conflicts of interest.

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