

# RESEARCH PROJECTS

## Biochemical urine analysis may boost adherence to treatment with blood pressure medications: the OUTREACH trial

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Adherence is defined by the World Health Organization as “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”.<sup>1</sup> Suboptimal adherence to prescribed blood pressure (BP) lowering medications hinders the treatment of hypertension and remains a major obstacle to effective BP control. This translates into increased cardiovascular risk, excessive healthcare costs, and unnecessary treatment escalations. It is a problem affecting up to one in three to four people with treated hypertension<sup>2-6</sup> and limits the effectiveness of guideline-based treatment.

### Detecting non-adherence to medication

Using an objective method of detecting non-adherence to medications has been identified as potentially useful as both a diagnostic test and a powerful therapeutic intervention when combined with a structured discussion targeting the key drivers on non-adherence.<sup>4</sup>

Chemical adherence testing (CAT), based on biochemical analysis of urine or blood samples for metabolites of BP-lowering medications may

be a practical component of this therapeutic intervention, and has already been recognised by international guidelines as an objective method for diagnosing non-adherence to therapy.<sup>7</sup> CAT uses high-performance liquid chromatography-mass spectrometry (HPLC/MS) to detect the presence of antihypertensive drugs or their metabolites in biological samples.

Observational studies have demonstrated a relationship between biochemical non-adherence and elevated BP, with increasing degrees of non-adherence associated with progressively poorer BP control.<sup>2</sup> Until recently, the clinical utility and cost-effectiveness of a CAT-guided intervention had not been evaluated in a prospective randomised controlled trial (RCT).



## Investigating the efficacy of urine CAT for non-adherence to BP-lowering medication

The OUTREACH study (BiOmarkers in Urine, anTihyperTensive trEAtment and blood pressure Control in Hypertensive patients)<sup>8</sup> was designed to address some of the existing gaps in knowledge in management of non-adherence to antihypertensive treatment. The study examined whether providing non-adherent hypertensive patients with information about their urine CAT test results, combined with a tailored discussion focussing on the main reasons driving their non-adherence (urine CAT-guided intervention), could lead to improved adherence and BP control compared with standard care (**Figure 1**).

Funded by British Heart Foundation, NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, and Omron, OUTREACH was a multicentre RCT conducted across 12 NHS sites in England and Scotland. We recruited adults with hypertension who had been prescribed at least two antihypertensive medications. At screening, patients found to be non-adherent to one or more prescribed medications were eligible for enrolment.

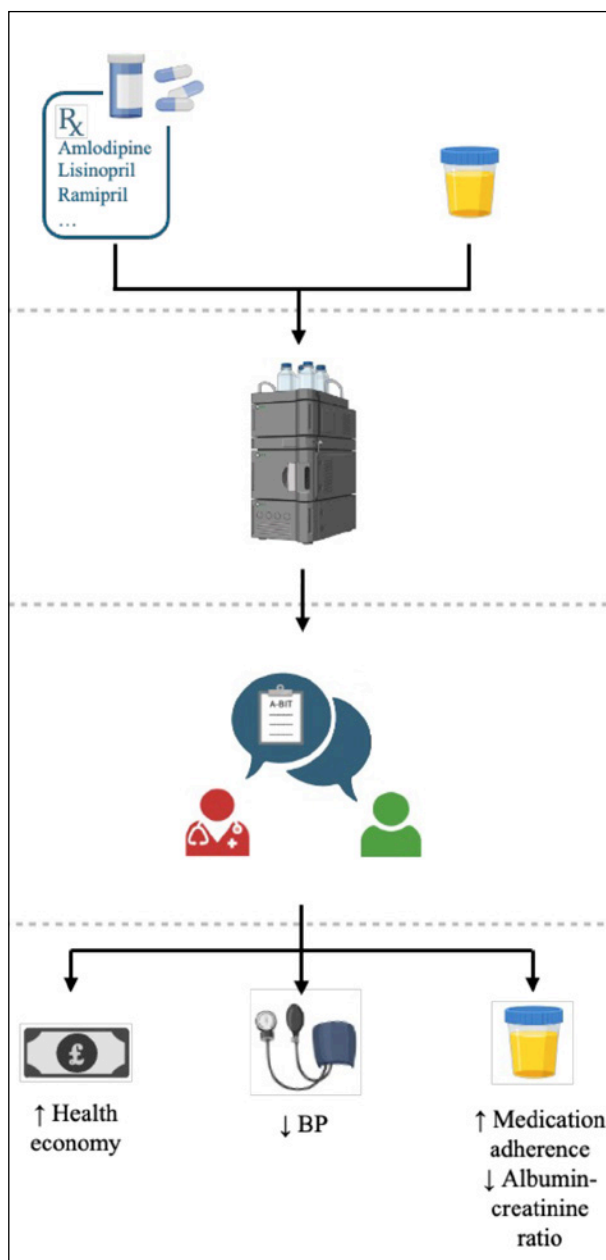
OUTREACH randomised a total of 130 participants to receive either CAT-guided intervention, consisting of disclosure of adherence-testing results alongside a structured discussion exploring reasons for non-adherence (group A), or to continue treatment according to standard clinical care (group B).

The intervention (delivered by trained physicians) aimed to identify and address individual barriers to treatment adherence, including concerns regarding adverse effects, treatment burden, medication beliefs, or practical difficulties with taking prescribed therapy.

### Promising improvement in medication adherence

Participants were followed up for a median of 2.8 months to assessment of the primary endpoint, and 4.7 months for longer-term secondary outcome evaluation. The primary endpoint was change in clinic systolic blood pressure (SBP) from baseline.

**Figure 1.** Study concept. The depiction of the study's overarching hypothesis; BP-blood pressure. Created with BioRender.com.



Secondary endpoints included biochemical adherence status, clinic diastolic BP, home BP measurements, urinary albumin:creatinine ratio (ACR), and health economic outcomes.

Whilst OUTREACH did not demonstrate a statistically significant difference in average SBP between the two groups at the primary endpoint, the adjusted SBP in those who received the CAT intervention was approximately 5 mmHg lower than in the standard of care group ( $p=0.19$ ). Other BP measures, including DBP and home

BP measurements were numerically consistent but did not reach the threshold of statistical significance.

We did, however, find a modest improvement in biochemical adherence to antihypertensive treatment at visit 4 (adjusted mean difference 12.7% [95% CI 0.9 to 24.4];  $p=0.035$ ). This is consistent with other studies which showed that CAT coupled with a structured intervention has potential to impact adherence.<sup>4, 9-11</sup>

## Limitations

OUTREACH was a very difficult trial to conduct. Recruitment reached only 80% of the planned target sample size. As with many clinical studies conducted during the early 2020s, the COVID-19 pandemic significantly affected recruitment, finances, staffing, participant follow-up, and study delivery. Protocol adaptations were necessary to facilitate safe participant attendance, and the study had to be paused and reactivated several times. Furthermore, recruitment and retention of patients with documented medication non-adherence presents well-recognised challenges for clinical trials and may have contributed to the lower-than-anticipated completion rates.

## Lessons from the trial

The OUTREACH study shows how to address common sources of bias when running RCTs on adherence to treatment. This includes the importance of mitigating against Hawthorne effect (an awareness of being monitored). We made sure to account for this effect by not giving participants advance warning of trial participation and including a second additional phenotyping visit to quantify how information about the trial may change adherence.

We also emphasise the importance of creating a strategy to ensure that over-delivery of the intervention is not inadvertently administered. Given the nature of the trial, we had anticipated that clinicians may go beyond their normal actions in particular in the standard of care arm. Therefore, we included a population of adherent participants (group C) in order to mask clinicians to the adherence status of participants allocated to this arm of the study.

Furthermore, we also identified a gap regarding a lack of guidelines for clinicians delivering results from a urine CAT. We developed our A-BIT tool to provide a structured conversation guide for clinicians to support the delivery of intervention. Our A-BIT tool was informed by the principles of NICE guidelines and was developed in collaboration with hypertension specialists, health psychologists, and patients with hypertension – it provides a guide on how to combine the results of urine CAT with a discussion tailored to patient needs. This ensured reproducibility in the care provided and is shared as a resource in our publication.

Finally, as part of the visits, OUTREACH participants completed deep psychological phenotyping. This information will be used in secondary analyses dedicated to understanding the psychological aspects of adherence.

## Conclusion

OUTREACH demonstrates that larger-scale trials are now required to fully understand whether CAT-based improvements in adherence can be translated into sustained BP reductions, improved cardiovascular outcomes, and long-term cost-effectiveness for people with hypertension. We would recommend that future RCTs should focus on recruiting participants from even larger number of centres run by teams experienced in dealing with non-adherent participants in order to effectively evaluate the full potential conferred by CAT-based intervention. A high degree of flexibility is required, and a longer duration should also be a priority. We deliver further practical insights for other investigators in our Lancet Primary Care paper.<sup>8</sup>

\*The main results of this study have been published here: Tomaszewski M, Gupta P, Chowienczyk P, et al. Chemical adherence testing-guided intervention versus standard of care in patients with hypertension who are non-adherent to antihypertensive treatment in the UK (OUTREACH): a multicentre, randomised controlled trial. The Lancet Primary Care. 2026;2(5):100154. doi:10.1016/j.lanprc.2026.100154

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