Take-home naloxone in multicentre emergency settings: the TIME feasibility cluster RCT

Helen Snooks,[1*] Jonathan Benger,[2] Fiona Bell,[3] Sarah Black,[4] Simon Dixon,[5] Helena Emery,[1] Bridie Angela Evans,[1] Gordon Fuller,[5] Rebecca Hoskins,[2] Jane Hughes,[5] Jenna Jones,[1] Matthew Jones,[1] Sasha Johnston,[4] Jaqui Long,[5] Chris Moore,[6] Rakshita Parab,[1] Richard Pilbery,[3] Fiona C Sampson[5] and Alan Watkins[1]

[1]Department of Medicine, Swansea University, Swansea, UK
[2]University of the West of England, Bristol, UK
[3]Yorkshire Ambulance Service, Wakefield, UK
[4]South Western Ambulance Services NHS Foundation Trust, Exeter, UK
[5]Sheffield Centre for Health and Related Research, University of Sheffield, Sheffield, UK
[6]Welsh Ambulance Services NHS Trust, Cardiff, UK

[*]Corresponding author H.A.Snooks@Swansea.ac.uk

Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Published October 2024
DOI: 10.3310/YNRC8249

Scientific summary

Take-home naloxone in multicentre emergency settings: the TIME feasibility cluster RCT

Health Technology Assessment 2024; Vol. 28: No. 74
DOI: 10.3310/YNRC8249

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Opioids, such as heroin, kill more people worldwide by overdose than any other type of drug, and death rates associated with opioid poisoning in the United Kingdom (UK) are at record levels. Naloxone is an opioid antagonist which can be distributed in 'kits' for administration by witnesses in an overdose emergency. This intervention is known as take-home naloxone (THN). We know that THN can save lives on an individual level, but there is currently limited evidence about the effectiveness of THN distribution on an aggregate level, in specialist drug service settings or in emergency service (ES) settings. Notably, we do not know whether THN kits reduce deaths from opioid overdose in at-risk populations, if there are unforeseen harms associated with THN distribution or if THN is cost-effective. To address this research gap, we aimed to determine the feasibility of a fully powered cluster randomised controlled trial (RCT) of THN distribution in emergency settings.

Aim

To determine the feasibility of carrying out a definitive RCT of THN in emergency settings.

Objectives

To determine:

1. the best form of THN kit, training and delivery
2. whether a trial clustered by emergency department (ED) catchment area and the associated ambulance service (AS) is deliverable, as assessed against predefined progression criteria related to intervention, trial design and methods.

Design

We assessed feasibility of intervention and trial methods based upon the following predetermined progression criteria.

Intervention feasibility

1. Sign-up of four sites, including ≥ 50% eligible staff to complete training in delivering the intervention at each intervention site.
2. Identification of ≥ 75% of people who have presented to ED or AS with opioid overdose or an opioid use-related problem over a 12-month period.

3. THN kits issued to ≥ 50% eligible patients over a 12-month period at intervention sites.
4. Serious adverse event rate [to be defined in agreement with Data Monitoring and Ethics Committee (DMEC)] of no more than 10% difference in intervention sites to control sites at the conclusion of recruitment.

Trial methods feasibility

5. Identification and inclusion for follow-up of ≥ 75% of people who died of opioid poisoning in the following year in the study areas according to Office of National Statistics (ONS) mortality data (previous ONS data suggest between 140 and 180 such deaths across the 4 participating sites during the study period).
6. Matching and data linkage in ≥ 90% of cases not dissented at the conclusion of quantitative data collection.
7. Retrieval of primary and secondary outcomes from National Health Service (NHS) Digital and National Welsh Informatics Service within 6 months of projected timeline.

As the intervention tested is for administration to recipients of the THN kits and peers who may suffer an overdose, we needed to find a way to identify cohorts to include in outcome comparisons. We therefore analysed Welsh routine data to test the feasibility of developing a discriminant function to identify a high-risk population for fatal opioid overdose. We scoped anonymised routine retrospective data from 1 January 2015 to 30 November 2021, sourced from the Welsh Demographic Service Dataset (WDSD) to define the study population. To categorise death associated with an opioid overdose, the annual district death extract (ADDE) dataset was used in conjunction with the WDSD to calculate an individual-level study end date. Finally, we considered critical care, ED and hospital admissions as well as substance misuse treatment for the 36 months up to the end of the study period.

We carried out a RCT clustered by site in the emergency environment with a qualitative study to examine processes of implementation, patient safety, costs of training NHS staff and experiences of service users and providers. Two intervention sites (paired ED and local AS catchment area) were randomly selected from the four participating sites. Usual practice was continued in the other two sites, acting as controls.

Alongside the RCT, we collected qualitative data via semistructured interviews with service users from substance use treatment centres and third-sector organisations. The interview questions were guided by literature around opioid overdose experience and emergency naloxone use, with the aim to explore how opioid users interact with the knowledge, behaviour and attitudes towards the use of THN kits and training to use the kits. Focus groups and interviews with service providers (paramedics and ED clinical staff) were conducted to discuss barriers in the provision of THN in the emergency setting as well as facilitators to this implementation.

We assessed the feasibility of collecting costs associated with THN provision in the emergency setting by measuring the health service contacts and incorporating healthcare resource groups (HRGs) into the analysis to produce an overall cost.

Setting

This feasibility study was carried out in the emergency care environment, across study sites each centred on a receiving ED and defined geographically as the local AS catchment area for that receiving ED.

Participants

At intervention sites, we invited ED clinicians and paramedics to participate in the trial and recruited adult patients who arrived at the ED or were attended by ambulance paramedics for a problem related to opioid use with capacity to consent to receiving the THN and related training.

Participants were to be identified for outcome comparison by application of the discriminant function, if completed, to the study site general populations.

Interventions

Usual care comprised administration of basic life support plus naloxone by paramedics or ED staff.

The THN intervention was offered in addition to usual care and included a multi dose THN kit (Prenoxad) containing 2 mg naloxone hydrochloride 1 mg/1 ml solution for intramuscular (IM) injection, and instructions on the correct administration of the naloxone dose. Recipients also received guidance on: BLS; the importance of calling the ES; duration of effect; the safety of naloxone in terms of adverse events and overdose; and the legality of bystander administration of naloxone.

Results

TABLE S1 Assessment against preset progression criteria

Criteria	Achieved	Criteria met
Sign-up of four sites, including ≥ 50% eligible staff to complete training in delivering the intervention at each intervention site	Site 1: ED trained 81.1%, AS trained 54% of eligible staff Site 2: ED trained 8.1%, AS trained 33.8% of eligible staff	No
Identification of ≥ 75% of people who have presented to ED or AS with opioid overdose or an opioid use-related problem over a 12-month period	Unable to assess	Not known
THN kits issued to ≥ 50% eligible patients over a 12-month period at intervention sites	21.7% of eligible patients were given kits	No
Serious adverse event rate (to be defined in agreement with the DMEC) of no more than 10% difference in intervention sites to control sites at the conclusion of recruitment	No serious adverse events were reported	Yes
Identification and inclusion for follow-up of ≥ 75% of people who died of opioid poisoning in the following year in the study areas according to ONS mortality data (previous ONS data suggest between 140 and 180 such deaths across the four participating sites during the study period)	We were able to identify decedents from opioid poisoning in Wales but were unable to produce a discriminant function which included this group in a sufficiently small section of the general population, or to test these methods in a second population	No
Matching and data linkage in ≥ 90% of cases not dissented at the conclusion of quantitative data collection	Due to significant delays in permissions processes for routine- linked data retrieval from NHS Digital, and low administration of THN kits, we did not attempt to match and link records for patients recruited to the trial	No
Retrieval of routinely recorded primary and secondary outcomes from national repositories within six-months of projected timeline	Again, due to significant delays in permissions processes for routine- linked data retrieval, and low administration of THN kits, we did not attempt to retrieve routinely recorded primary and secondary outcomes	No

Discriminant function

With low numbers of opioid-related deaths (1105/3,227,396) and a high proportion of them having no contact with health services in the year before death, the predictive link between death and opioid-related healthcare events was weak. Logistic regression models indicated we would need to monitor one-third of the population to capture 75% of the decedents from opioid overdose in 1-year follow-up.

RCT

In total, 299 of 687 (43.5%) eligible staff were trained to supply THN kits to eligible patients at the two sites (Site 1: ED *n* = 107, AS *n* = 121; Site 2: ED *n* = 25, AS *n* = 46). Sixty THN kits were supplied to eligible patients during the recruitment period (Site 1: ED *n* = 36, AS *n* = 4; Site 2: ED *n* = 16, AS *n* = 4). Eligible patients were recorded as not being offered THN kits 164 times, with reasons reported for not offering eligible patients kits: staff forgot (*n* = 136); staff too busy (*n* = 15); and suspected intentional overdose (*n* = 3). Staff recorded 626 people as being considered for inclusion but found not to be eligible, with reasons listed as: uncooperative including being abusive towards staff (*n* = 55); lack of capacity (*n* = 35); reduced consciousness level (*n* = 41); patient in custody (*n* = 21); and patient absconded (*n* = 161).

Qualitative interviews

Service users had high levels of knowledge about THN, with variable previous access to kits. They generally supported the provision of THN kits and training in the emergency setting and felt that it should be expanded further to chemists and needle exchanges. They also noted the importance of including loved ones in training and felt that this gave them a sense of empowerment and motivation to help others in an overdose situation. They noted concerns with regards to opioid withdrawal and resistance to attending hospital for an overdose. The service users reported that the provision of THN kits and training to friends and family of opioid users would possibly be more beneficial and believed that incorporating THN provision into normal practice would help mitigate some of these barriers.

Interviews and focus groups with service providers found that they were supportive about the provision of THN kits and training in the emergency setting. However, they also reported barriers including difficulties consenting and training opioid users, a high turnover of staff impacting the cascade of the intervention as well as negative attitudes towards the patient group and the coronavirus disease 2019 (COVID-19) pandemic.

No adverse events were reported.

Conclusion

This study did not meet progression criteria for intervention or trial methods feasibility, so outcomes were not followed up and a fully powered trial is not planned.

There does appear to be appetite for THN kit provision and training in the emergency setting.
We conclude that the THN intervention as defined and administered in the Take-home naloxone Intervention Multicentre Emergency setting (TIME) study was not feasible and should not therefore go forward to full trial. However, there may be space for further development of this complex intervention in emergency care – for example, for protocols to allow administration to family and friends of opioid users; as well as methods for definition and identification of study cohorts for outcome comparisons.

Trial registration

This trial is registered as ISRCTN13232859.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 16/91/04) and is published in full in *Health Technology Assessment*; Vol. 28, No. 74. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.6

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.6 and is ranked 32nd (out of 105 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal
Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was funded by the HTA programme as award number 16/91/04. The contractual start date was in March 2018. The draft manuscript began editorial review in April 2023 and was accepted for publication in November 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).