Contemporary Clinical Trials Communications 5 (2017) 100–106

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

External data required timely response by the Trial Steering-Data Monitoring Committee for the NALoxone InVEstigation (N-ALIVE) pilot trial

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ARTICLE INFO

Article history:
Received 12 August 2016
Received in revised form
20 October 2016
Accepted 14 January 2017
Available online 18 January 2017

Keywords:
Data Monitoring Committee
Randomized pilot trial
External evidence
Elicitation
Causality
Cessation

ABSTRACT

The prison-based N-ALIVE pilot trial had undertaken to notify the Research Ethics Committee and participants if we had reason to believe that the N-ALIVE pilot trial would not proceed to the main trial. In this paper, we describe how external data for the third year of before/after evaluation from Scotland's National Naloxone Programme, a related public health policy, were anticipated by eliciting prior opinion about the Scottish results in the month prior to their release as official statistics. We summarise how deliberations by the N-ALIVE Trial Steering-Data Monitoring Committee (TS-DMC) on N-ALIVE's own interim data, together with those on naloxone-on-release (NOR) from Scotland, led to the decision to cease randomization in the N-ALIVE pilot trial and recommend to local Principal Investigators that NOR be offered to already-randomized prisoners who had not yet been released.

1. Introduction

Naloxone is an opioid antagonist used for emergency resuscitation following opioid overdose. Prisoners with a history of heroin use by injection have a high risk of drug-related death (DRDs) in the first weeks after release from prison [1,2,3]. The N-ALIVE trial was planned as a large prison-based randomized controlled trial (RCT) to test the effectiveness of Naloxone-on-release (NOR) in the prevention of fatal opiate overdoses soon after release (30% reduction in the first 4-weeks; 20% in weeks 5–12) [4]. The N-ALIVE pilot trial (ISRCTN34044390) was a randomized feasibility study to test the main trial's assumptions on recruitment of prisons and prisoners, and also the logistics for ensuring that randomized participants received their N-ALIVE pack on release [5]. See Meade et al. [6] for how delivery of the N-ALIVE protocol was achieved in 16 prisons in England. See Parmar et al. [5] for the feasibility outcomes in the N-ALIVE pilot trial. The N-ALIVE pilot trial had undertaken to notify the Research Ethics Committee and participants if we had reason to believe that the N-ALIVE pilot trial would not proceed to the N-ALIVE main trial.

The start of Scotland's National Naloxone Policy (NNP) in January 2011 [7], with funding for both NOR and community-based take-home naloxone (THN), had pre-empted the N-ALIVE trial's planned randomization in Scottish prisons. The primary outcome for Scotland's science-led NNP-evaluation [8] was a 20%–30% reduction in the proportion of opioid-related deaths (ORDs) with a 4-week antecedent of prison-release. As the proportion had been 10% in 2006–2010, Scotland's NNP had 80% power to discern reduction to 7% in 2011–13, as upper target; or to 8% in 2011–15, as lower target.

In this paper, we describe how external data for the third year of

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http://dx.doi.org/10.1016/j.conctc.2017.01.006

before/after evaluation of Scotland's NNP, a related public health policy [7–10], were anticipated by eliciting prior opinion about the Scottish results in the month prior to their release as official statistics [11,12]. We then describe how deliberations by N-ALIVE's Trial Steering-Data Monitoring Committee (TS-DMC) on N-ALIVE's own interim data, together with those on NOR from Scotland, led to the decision to cease randomization in the N-ALIVE pilot trial and to recommend to local Principal Investigators (PIs) that NOR be offered to already-randomized prisoners who had not yet been released [5].

To be ready to act promptly, we had elicited expert opinion about the Scotland's forthcoming results [11] in order to focus on the most probable scenarios for TS-DMC's decision-making. Unscheduled interim analysis was also undertaken of the N-ALIVE pilot trial's own data from returned prisoner self-questionnaires, specifically on the extent of NOR's administration intramuscularly to the ex-prisoner for whom it had been prescribed versus to another person.

We begin, therefore, with a brief history of formally eliciting prior opinion to inform the design and monitoring of RCTs funded by the UK's Medical Research Council (MRC); and some early accounts of DMC deliberations. The back-story on the NALoxone InVEstigation (N-ALIVE) follows, which puts our elicitation in context, and sets the scene for deliberations and decisions by the N-ALIVE's TS-DMC.

2. On elicitations for randomized trials funded by the Medical Research Council and deliberations by Data Monitoring Committees

The earliest example of formally eliciting prior opinion to inform trial design was “place your bets” about the mortality of surfactant-treated very premature babies (aged 25–29 weeks) in a RCT funded by MRC in the mid-1980s [13,14]. This “trial roulette” method was again used in the design and early stopping of the MRC's neutron therapy trial in pelvic cancer [15–18]: the minority prior belief on the relative mortality of neutrons versus photons turned out to have been consistent with trial's data. Following the early termination by the investigators of this neutron therapy trial, a decision later ratified by a specially-convened post-hoc DMC, the MRC required all of its RCTs to have a properly constituted DMC.

In 1994, Spiegelhalter, Freedman and Parmar [19] formalized Bayesian approaches to RCTs. Their Bayesian design and monitoring of the CHART trials included a description of how prior elicitation of clinicians' opinion could be used to form “enthusiastic” and “sceptical” prior distributions [20]. Neither CHART trial was closed to recruitment because, at each annual review, there was insufficient evidence to convert either the sceptics or the enthusiasts [21].

In 1999, on behalf of the Concorde, Alpha and Delta trials which randomized patients with asymptomatic HIV infection, Armitage (as DMC-chair) provided two insightful accounts of the DMC deliberations: the first on interpreting early data and trends in surrogate markers [22,23] and the second as clear-cut differences in efficacy gradually emerged [24]. See also Wittes [25]; Ellenberg, Fleming and DeMets [26] for an early practical textbook; and the injunction by Grant that DMCs must show strong resolve when large unanticipated differences are inconsistent with existing evidence from outside the RCT [27], as Goodman later endorsed [28].

By 2005, the DAMOCLES Study Group, like the MRC, had recommended that every RCT should have a DMC [29]; and proposed a DMC charter to help them do their job well [30]. Of 20 questions that DAMOCLES posed to 25 regulatory or funding organizations, the two least likely to be answered were: on the training of DMC members (2 responses) and on decision-making within DMCs (3 responses) [29]. For further examples of DMC decision-making, see both the DAMOCLES Study Group [29] itself (four examples) and Pocock's editorial on when (not) to stop a clinical trial for benefit [31], in which he discussed the merit of the Haybittle-Peto boundary which requires $P < 0.001$ as evidence to stop an RCT for efficacy.

Tharmanathan et al. [32] surveyed the use of interim data (with or without the mention of DMCs) by RCTs published in eight major journals: of 1772 RCTs published during 2000–2005, 470 (27%) reported the use of a DMC and a further 116 (7%) some form of interim analysis without explicit mention of a DMC; see also Sydes et al. [33] (for the DAMOCLES Study Group) who had contrasted DMC-mentions in 1990 versus 2000.

3. Back-story on the N-ALIVE pilot trial and Scotland's National Naloxone Policy

In late summer 2008, the MRC funded the pilot phase (that is: first 10% of randomizations) of the N-ALIVE Trial [4,5,6] which was to run in two prison jurisdictions (Scotland; England & Wales). Pro-rata in each jurisdiction, 2800 consented eligible prisoners with a history of heroin-injection were to be randomized during incarceration to receive their assigned N-ALIVE pack on-release. The trial was double-blind only until participants opened their assigned N-ALIVE pack immediately after release.

The randomization ratio was 1:1. The N-ALIVE control packs contained no syringe and no naloxone. The naloxone packs contained a syringe of naloxone for “rescue” injection in the event that the participant overdosed on opioids [1–3]. The syringe contained 2 mg of naloxone hydrochloride in 2 ml of solution, for once-only intramuscular (IM) injection in the event of overdose. During information and consent sessions while incarcerated, all N-ALIVE participants were advised on how to administer 0.8 mg of naloxone.

The N-ALIVE pilot trial was designed to investigate the feasibility of randomized provision of NOR to eligible prisoners. The definitive N-ALIVE Trial would determine if NOR reduced participants' drug-related deaths (DRDs) by 30% in the first 4-weeks after release and by 20% in the subsequent 8 weeks [4,5,6]. Per 2800 releases in the control group, we expected 14 DRDs in the first 4-weeks and 3.5 DRDs in the subsequent 8 weeks [4,5].

As high risk of overdose death soon after prison-release applies per-release, re-randomization was permitted provided that at least six months had elapsed since the participant's previous N-ALIVE release-date.

3.1. Contamination between randomized groups?

In designing the N-ALIVE pilot trial, we had anticipated contamination between randomized groups of up to 20% because participants who had been randomized to NOR might administer their naloxone alternatively to an opioid-dependent peer who had overdosed, some of whom - unknown to us - might have been randomized to N-ALIVE's control group.

Specifically, if ex-prisoners' 8 times higher DRD-risk in the first fortnight after release [1] was on account of an 8 times higher overdose-risk then, assuming that one of (say) three co-present injectors overdoses, there is an 80% chance that the person who overdosed was the recently-released ex-prisoner to whom naloxone (if also present) will therefore be administered.

However, if injectors' chance of opioid overdose is the same regardless of recent prison-release, so that recently-released ex-prisoners' DRD-risk is due to an 8 times higher fatality-rate per opioid overdose, then each of the injector-triad above has the same chance of opioid-overdose. In this scenario, there is potentially a two-thirds chance that the ex-prisoner's NOR is administered to another person so that contamination between N-ALIVE's