implementation of the intervention. A definitive RCT should take place only after the first two stages have been completed. Our experience in Bradford is that advance statements are complex interventions that require lengthy developmental work if they are to stand a chance of success. Papageorgiou *et al* make no reference to what, if any, developmental work took place before the introduction and evaluation of advance statements, making it difficult to draw conclusions about their effectiveness or otherwise.

Declaration of interest

P.T. is a grant co-holder with the Mental Health Foundation in the Advance Statement Project in Bradford, funded through section 64 funding by the Department of Health.

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Authors' reply: Dr Thomas is right to point up the difficulties of evaluating advance directives in mental health care. To answer their specific queries: (a) Who recruited patients? A psychologist (A.P.) and a psychiatrist (Anis Janmohamed) recruited the patients. (b) How did recruitment take place? The ward managers, responsible psychiatric nurses, junior doctors or consultants (depending on who was available at the time) were approached on a weekly basis and a list was drawn up of all patients who were near discharge from section. A.P. and A.J. introduced eligible patients to the trial and gave them a written summary of our aims and procedures. Patients were given time to read the summary and decide whether they wanted to participate in the study. Those who agreed undertook a baseline assessment and were randomised into the experimental and control group. (c) What steps were taken to inform the service users about the pros and cons of advance statements? The participants were seen individually by A.P. and A.J., who informed them about the advantages and disadvantages of advance directives. Participants were also informed about accessibility of their local service users' groups for further advice on any related issues. (d) How were service users, professionals and structures of care such as the Care Programme Approach process prepared for advance statements? The lead academic (M.K.) had extensive discussions with managers, consultant psychiatrists and nurse managers about the study to ensure they were fully informed and prepared for the trial. Although it would have been useful to incorporate the directives into the formal Care Programme Approach process, clinicians did not think that this was warranted at that stage. Local service users' groups were informed about the study, and A.P. and M.K. talked to the groups regularly throughout and after the trial. M.K. leads a collaborative group in north London between service users and academics to promote user-led research. We considered it a strength of our trial that participants prepared their directives with someone who was ***not*** involved in their care, as this made the whole process less open to duress. (e) Do professionals really consider advance statements to be useful and take their implementation seriously? Professionals certainly took the intervention seriously at meetings and presentations where the study was discussed and readily agreed to the trial. However, by the end of the trial they were unsure about the value of the directives, a finding that we discuss in a further paper that has been submitted for publication (further details available upon request). (f) Was there developmental work before the introduction and evaluation of advance statements? Considerable work with users and professionals was carried out before the trial commenced to develop the format of the advance directive. However, as Dr Thomas will know, obtaining funds for this valuable work is extremely difficult, and thus it was limited. During our developmental work, we became more aware of the legal complexities of advance directives and the possibility that they could be considered binding on clinicians. Because their worth was at this stage unproven, we took the step of including a clause stating that users' wishes could be overridden. We concur with Dr Thomas's views on the Medical Research Council's framework for the evaluation of complex interventions. However, when our study was conceived in 1996 these recommendations were not available. The pre-clinical justification for the study was increasing use of advance directives in this country and in the USA. Given the mood of the time, our study was justified.

We made it clear in our paper that we did not consider our study definitive. We would welcome further research on the additional matters raised and hope our study stimulates such work. We acknowledge that our study does not evaluate the effectiveness of advance directives under optimum conditions – in fact, that was not our aim. Ours was a pragmatic trial in which we sought to assess whether such directives were useful in a real, inner-city clinical setting. We used rates of compulsory readmission as our main outcome measure to test one bold claim made for them, namely that they may reduce the need for patients to be civilly committed at a later time. If substantiated, this is a very important matter.

Advance directives may be a useful expression of patient autonomy and self-direction. We look forward to reading the results of further research.

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Rivastigmine and QT interval prolongation

Walsh & Dourish (2002) reported that a 78-year-old man, receiving a number of medications and with a history of myocardial infarction and hypokalaemia, developed an abnormal QTc interval a week after starting rivastigmine treatment. I have performed an extensive review of the tolerability and safety of cholinesterase inhibitors (Inglis, 2002), in which I described the favourable cardiac safety profile of rivastigmine. Therefore, I contacted Novartis for more information. This case, which was initially submitted to the authorities in June 2001, included further clinically relevant information.

Primarily, the patient's pre-rivastigmine QTc (3 weeks before starting treatment) was 431 ms rather than 397 ms as suggested by Walsh & Dourish (C. Videbaek (Novartis), personal communication, 2002). The reported QTc of 397 ms was obtained a week after starting rivastigmine

https://doi.org/10.1192/bjp.182.6.549 Published online by Cambridge University Press

treatment, indicating that during this week the patient's electrocardiogram (ECG) 'normalised'. The following week (2 weeks post-rivastigmine) it increased to 477 ms. The QTc prolongation (pre-rivastigmine to 2 weeks post-rivastigmine) was less than 11%. Nevertheless, since this change was above the 30 ms usually considered relevant, it is important to assess in an unbiased manner whether it was drug-induced.

The patient was already at risk of cardiac abnormalities owing to: previous increased QTc; hypokalaemia (a risk factor for QTc change; De Ponti *et al*, 2002) 2 weeks before starting rivastigmine treatment (no potassium values were reported at the time of the ECG finding); concomitant use of diltiazem, which is known to cause atrio-ventricular blockade and bradycardia (risk factors for QTc change; De Ponti *et al*, 2002); a history of hypertension, ischaemic heart disease, myocardial infarction and cerebrovascular accident, reflecting the presence of clinically significant heart disease (another risk factor for QTc change; De Ponti *et al*, 2002): concurrent Lewy body dementia, which is associated with autonomic failure (McKeith, 2000) and frontal lobe deficits that may influence QT intervals (Kubota *et al*, 2001).

My review of the cholinesterase inhibitors (Inglis, 2002) included an analysis of 2791 patients involved in pivotal studies of rivastigmine in Alzheimer's disease (Morganroth *et al*, 2002). About 30% and 10% of these patients had cardiovascular disorders and heart rate/rhythm disorders, respectively. About 35% were receiving concomitant cardiovascular treatments. Even in this relatively at-risk population, heart rate, PQ, PR, QT and QRS intervals were very similar in rivastigmine- and placebo-treated patients, indicating that rivastigmine did not produce adverse effects on cardiac function as assessed by ECG. The lack of cardiac effects associated with rivastigmine may be explained by its selectivity for central over peripheral cholinesterases, and an apparent brain-region selectivity that may avoid areas such as the medullary cardiorespiratory nucleus (Enz *et al*, 1993).

Case reports are an important means of communicating clinical observations. However, it is important that the facts are presented clearly to allow a balanced judgement on the available evidence. I would suggest that the prolonged QTc described in this single case report is more likely to be due to the confounding factors described above than to a causal association with rivastigmine treatment. The cholinesterase inhibitors form an invaluable part of our limited armamentarium in managing patients with dementia. It would be unfortunate if patients who might benefit from these treatments were deprived of them because of false-positive associations with cardiotoxicity.

Declaration of interest

F.I. has conducted research for and been supported by research grants from Janssen-Cilag, Novartis Pharmaceuticals and Shire Pharmaceuticals. He has lectured for Janssen-Cilag and is a member of the Novartis Speakers Bureau.

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Author's reply: Prolonged QTc interval is defined as a QTc longer than 440 ms (Khan, 2002); therefore, by this definition, the patient did not have a documented prolonged QTc interval prior to the introduction of rivastigmine.

As detailed in the original report of this case to Novartis, the patient had been admitted a number of weeks previously to a medical ward where he developed diarrhoea which was deemed responsible for the lowering of his potassium. As a result he received potassium supplements while the diarrhoea was ongoing and once the diarrhoea stopped the potassium was rechecked and the potassium supplements were discontinued. The patient had no diarrhoea at any stage during his treatment with rivastigmine that could have led to a further development of hypokalaemia. The patient had been receiving his other medications on a long-standing basis, including diltiazem for 5 years, and electrolytes checked intermittently had not shown previous problems with hypokalaemia. It is therefore unlikely that the patient was hypokalaemic at the time of the prolonged QTc interval.

The patient had no recent history of cardiac abnormalities apart from a myocardial infarct 6 years previously and long-standing hypertension. The patient had been on long-standing medication and there was no evidence of a prolonged QTc while on these medications. Although the patient had symptoms suggestive of dementia with Lewy bodies he did not fulfil the criteria for a diagnosis of probable dementia with Lewy bodies (McKeith *et al*, 1996).

In conclusion, this patient had evidence of a normal QTc interval prior to the introduction of the rivastigmine and developed a prolonged QTc while on the treatment which reverted to normal on discontinuation of the drug. His concomitant medication had been long-standing, he had no recent history of cardiac abnormalities and his previous hypokalaemia secondary to diarrhoea had been corrected. Therefore, we suggest there is a possibility of a causal relationship between rivastigmine and prolonged QTc interval. Independently, Novartis have received two isolated reports of QT interval prolongation, which the company have attributed to confounding factors such as co-medication and electrolyte abnormalities as well as insufficient/discrepancies in documentation (J. Collins (Novartis), personal communication, 2001).

I agree with Dr Inglis that the cholinesterase inhibitors are an invaluable part of our limited armamentarium in managing people with dementia but as with any new treatment only when a large number of patients are treated, many of whom will be taking multiple medications, have different comorbidities and be subject to other conditions that were not represented in the original trial population, will adverse effects become manifest that were otherwise not recognised, appreciated or expected. It is important that clinicians

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