Research Protocol (**version 2.1, 27th May 2014**)

DRIE 2 Protocol (Dehydration Recognition In our Elders, Re-test)

Testing of a simple tool for diagnosis of water-loss dehydration: a diagnostic accuracy study.

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Research sites: the research will be carried out within care homes in Norfolk and Suffolk, UK

Samples will be analysed in the pathology laboratory of the Norfolk & Norwich University Hospital, Norwich Research Park, Norwich NR4 7UY, Norfolk, England, contact Sue Kerry (01603 646545).

Ethics Committee: National Research Ethics Service Committee Wales REC 7 (14/WA/0145, 25th April 2014).

Steering Committee:

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DRIE website: the DRIE study website provides further information on the study, including information on the steering committee and participating care homes. See http://driestudy.appspot.com/

ISRCTN registration: ISRCTN58315094, see http://controlled-trials.com/ISRCTN58315094

Study summary for DRIE 2

Dehydration in older people is associated with risk of poor health outcomes such as falls, heart disease, confusion, pressure ulcers, poor wound healing, infections, drug toxicity and poor quality of life. High quality cohort studies, adjusted for important confounders, have found that dehydration is predictive of mortality and disability in a range of populations (1-3). Early identification, prevention and treatment of dehydration in the community would be good for older people and reduce NHS costs. As assessment of blood osmolality (a good measure of water-loss hydration, associated with insufficient fluid intake, which represents the concentration of some of the components of the blood) is not commonly available in residential care, so a simple tool (a short decision tree of tests) that could be carried out day to day by care home staff, that accurately indicates hydration status, is desirable.

Our earlier study, DRIE, interviewed 200 older people living in care homes, assessed their hydration status and carried out a range of tests and assessments that might indicate hydration status. We analysed these data on potential signs, conditions and tests, and found that no single test or sign was usefully diagnostic in its own right. As a result, we produced several possible decision trees that could be used in residential care to identify dehydration. Decision trees have the ability to minimise testing for the individual, while accurately predicting hydration status. This research, DRIE 2, aims to test the two best decision trees in a second group of older people living in residential care.

We will recruit 200 older people living in residential care (where dehydration is common). We will test for water-loss dehydration (through blood osmolality) and also carry out the assessments needed for the decision trees, as well as collecting health and demographic information. We will use these data to assess diagnostic accuracy of the proposed decision trees to diagnose or rule out dehydration.

Background

The study purpose is to test 2 tools (decision trees) that we have recently developed to diagnose water-loss dehydration in older people.

Justification:
Dehydration in older people is associated with high levels of risk of adverse health outcomes and death (4;5), and contributes to many major causes of death and morbidity, including falls, heart disease, confusion, constipation, renal failure, pressure ulcers, poor wound healing, infections, drug toxicity, and poor quality of life (6-13). Prospective studies that adjusted appropriately for concurrent risk factors and disease have suggested that raised serum osmolality and/or tonicity are associated with increased risk of mortality in a general elderly US population, UK stroke patients and US older people with diabetes, and that raised tonicity is associated with poorer functional status in US older people (1-3). For example, in 561 non-disabled people aged at least 70 years increased tonicity (≥300 mOsm/L) compared to normal tonicity (285-294 mOsm/L) was associated with a doubled risk of disability at 4 years (RR 2.1, 95% CI 1.2 to 3.6) (1). This analysis controlled for age, sex, race, weight, smoking, activity, plasma urea and creatinine, cognitive impairment, depression, and chronic disease. The relationship between raised tonicity and mortality at 8 years was also assessed, finding a 40% increase in risk of 8-year mortality (RR 1.4, 95% CI 1.0–1.9) (1).

John Reid, Secretary of State for Health, stated that high numbers of unplanned hospital admissions in the "at-risk elderly" were for entirely preventable conditions such as dehydration (14). In the US the estimated avoidable cost to the 1999 US healthcare system of older people admitted to hospital with a primary diagnosis of dehydration was $1.1 to $1.4 billion annually, and hospitalisation rates appear to be rising (15) with estimated costs in 2004 at $5.5 billion (16). Early identification, prevention and treatment of dehydration in the community would be good for older people and reduce NHS costs.

Dehydration is a complex condition resulting in a reduction in total body water (9), including water loss dehydration (due to water deficit, which can be hypernatraemic or hyponatraemic in the presence of hyperglycaemia) and salt loss dehydration (due to salt and water deficit, generally hyponatraemic, rarely isotonic). The reference standard for water loss dehydration is debated. While serum osmolality is a strong contender, disadvantages include slow response to dehydration and rehydration (17), but these are outweighed by its advantages. Advantages include that it can be measured at a single assessment (change in weight over a short period signals change in hydration but requires assessment over several days), is associated with health outcomes, and directly measures amounts of effective solute in plasma - as these solutes are relatively impermeable to cell membranes they influence cell volume via their osmotic force on cells. Abnormally raised osmolality implies dysregulation in multiple organ systems, and cell dehydration as intracellular fluid moves to extracellular space to reduce the osmolality, shrinking the cells (8;18). Salt loss and isotonic dehydration are also important, but differ from water-loss dehydration, requiring distinct treatment (with isotonic fluids). Hyponatraemia is less common and less predictive of outcome than increased osmolality in older people (associated with 25% increase in 5-year mortality (5)), so needs to be studied separately (9).

Current dehydration (serum osmolality >300 mOsm/kg), which develops following impending dehydration (295-300 mOsm/kg), can be a medical emergency and 17% of those admitted to hospital with a main diagnosis of dehydration die within 30 days (5). If we can diagnose current dehydration this may help us act to reverse it, improve quality of life and wellbeing for older people and reduce health costs. For these reasons this research will focus on water-loss dehydration, with serum osmolality as reference standard.

Dehydration prevalence in frail older people varies by setting, level of care required, social deprivation and how hydration status is assessed. 4% of the growing number of older people in the UK live in a care home or long-stay hospital (rising to 21% of those aged 85+) – this is an extremely frail population (19). In Norfolk care homes we found that on a single assessment 30% of 56 residents living in six care homes were dehydrated (with a furrowed tongue) (20), while a Californian nursing home study found 31% dehydrated at some point over 6 months (21). In the pre-cursor to this study, the original Dehydration Recognition in our Elders (DRIE) study, we found that of the 200 older people interviewed, 195 had useable serum osmolality data (2 were excluded as we found out after the interview that they had congestive heart failure, and 3 had lab errors on serum osmolality measures). At this single point in time 7 participants (4%) had low serum osmolality (<275mOsm/kg, and so were omitted from our analyses to determine a decision tree), 98 (50%) were euhydrated (275 to <295 mOsm/kg), 52 (27%) had impending dehydration (295 to 300 mOsm/kg) and 38 (19%) had current dehydration (serum osmolality >300mOsm/kg).

Dehydration is more common as we age as our thirst response (22) and total body water (TBW) both reduce (13;23), and medications and increased dependence on carers increase dehydration risk (10). Contributors to low fluid intakes include clinical (dysphagia, functional impairment, dementia, and pain), social (lack of attention to drink preferences, inability of residents to communicate with staff, and lack of social support) and institutional factors (untrained and unsupervised staff) (18). Issues around incontinence and access to the toilet are also important issues in older people's decisions around drinking (according to comments from DRIE care home resident and care staff advisory group members). Water-loss dehydration, like falls or anaemia where identified, needs to be investigated to assess its causes, before addressing underlying problems. Where reduced fluid intake or increased losses are indicated, suggested interventions to prevent or reverse dehydration in older adults living in care homes include education and involvement of care staff, use of social times, drinks carts and water jugs, encouraging relatives to drink with residents, monitoring urine colour, improved toileting support and supporting those with swallowing problems (6;10).

To protect the health of care home residents, and prevent emergency hospital admissions, care staff must recognise and treat water-loss dehydration. Serum osmolality, though the best indicator of water-loss dehydration, is too invasive for day to day monitoring in residential care (24). Clinical signs are commonly used to diagnose dehydration, but there is doubt about the diagnostic accuracy of many commonly used signs in older people (though effective in children and younger adults). A systematic review of the diagnostic accuracy of physical signs of hypovolaemia, which included studies published up to late 1997, found that in the few relevant studies there was limited evidence that in older people with vomiting, diarrhoea or reduced fluid intake that dry axilla supported the diagnosis of hypovolaemia, while moist mucous membranes or a tongue without furrows supported lack of hypovolaemia. Capillary refill time and poor skin turgor were not diagnostic in older people (25). An Australian cohort found that orthostatic blood pressure drop, sternal skin turgor, tongue dryness and body mass index were good indicators of early dehydration, but assessed against a reference standard of physician diagnosis (made using the very signs being tested (index tests), so were potentially biased) (26).

We recently completed and submitted a Cochrane diagnostic accuracy systematic review to assess clinical and physical signs for diagnosis of dehydration in older people (27;28). As only 3 relevant studies had been fully published (assessing the relationship we are interested in, and providing a 2x2 table needed to run our analyses) we collected data sets with the required data and re-analysed them to provide the information we need. We collected 21 full data sets, including data on well over 2000 older people aged 65+. Sixty seven tests were assessed (often at three cut offs) for diagnostic accuracy of impending and also of current dehydration. The only tests to show any ability to diagnose water-loss dehydration as stand-alone tests were expressing fatigue,

missing some drinks between meals and bioelectrical impedance analysis (BIA) resistance at 50kHz. In secondary analyses drinks intake, urine osmolality and axillar moisture also showed limited diagnostic accuracy. However, missing drinks between meals was assessed in only one small study, and for the other measures additional studies using the same measures did not suggest similar diagnostic utility. There was enough evidence to suggest that several stand-alone tests that are often used to assess dehydration in older people (including fluid intake, urine specific gravity, urine colour, urine osmolality, urine volume, heart rate, dry mouth, feeling thirsty and BIA total body water, intracellular water and extracellular water) are not useful, and should not be relied on individually as ways of assessing presence or absence of dehydration in older people. A variety of the measures assessed within the systematic review, as well as measures from existing tools for diagnosing dehydration in children (29) and measures used by healthcare professions but not formally tested previously were assessed in the original DRIE study (assessed against serum osmolality). These data will be added to the first update of the systematic review in 2014/15, but did not confirm that expressing fatigue was a good indicator of dehydration in a care home population, and missing drinks between meals had some limited utility (although only the question on whether residents always drink in the morning was useful enough to become part of the final decision tree).

In DRIE we found that no individual test, sign or question was usefully diagnostic of either impending or current dehydration on its own, so we developed and tested a set of decision trees. The most robust tree (decision tree 1), that identifies people with current dehydration and has an acceptable diagnostic accuracy includes allows every care home resident to be classified as dehydrated or euhydrated with a maximum of 3 questions. These include

1. Does the older person use diabetic medication?
2. When asked whether they have a drink first thing in the morning (before breakfast) do they answer yes, no, or are unsure or are unable to answer?
3. What is their change in diastolic blood pressure from sitting (for at least 10 minutes) to 3 minutes after standing up (with support if needed), or are they not able to stand for 3 minutes?

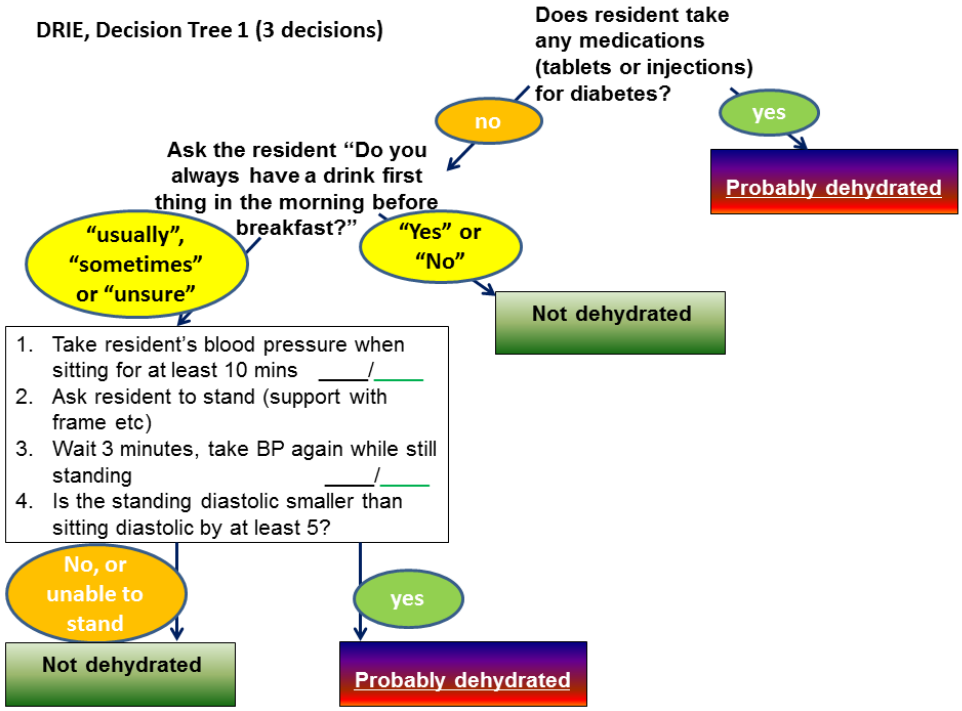

Figure 1. Decision tree 1

Several decision trees, which worked nearly as well as decision tree 1, included the same or similar tests/questions in slightly different orders. The next best tree for diagnosing current dehydration, that included different tests and questions, was decision tree 2.

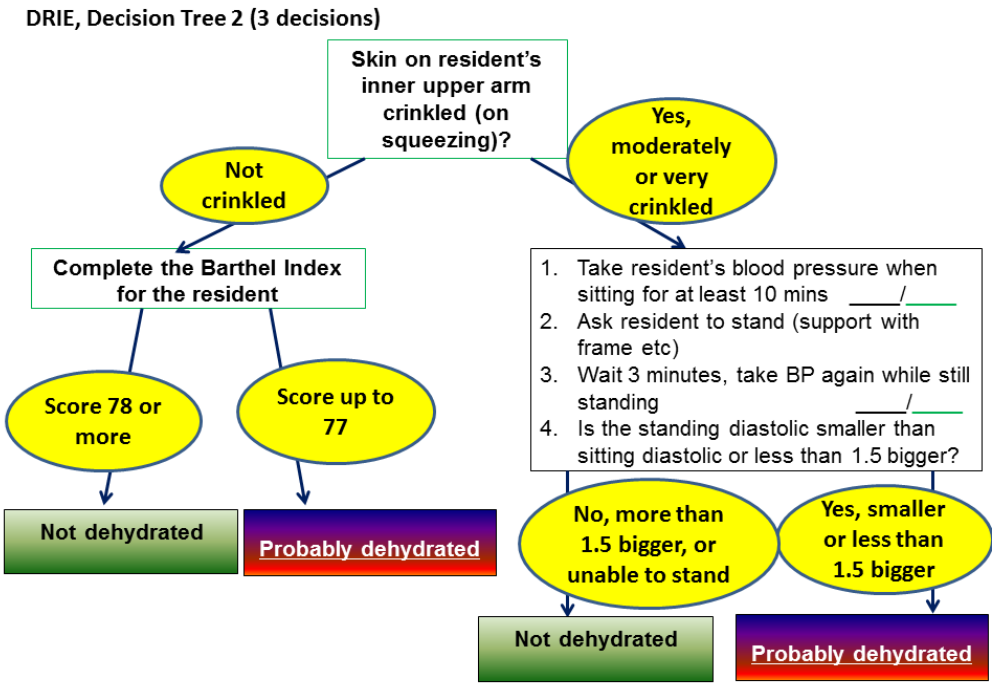

Figure 2. Decision tree 2

We have discussed the utility of these two decision trees with one of our care home staff advisory groups, and with a large group of care home managers and staff (at an ENRICH meeting where we discussed our research and some of the findings of the DRIE study, Norwich 3rd March 2014). The staff felt that these two decision trees would be feasible to use in everyday practice in a care home, and would like us to provide pictures of how to assess crinkling on the arm. Some managers of residential (not nursing) homes were concerned that their staff do not usually measure blood pressure so their staff would need good training, and also clear instructions about what blood pressure readings need to be reported to the GP (as they indicate worryingly high or low readings generally, as opposed to being relevant to hydration status). These are all good points. Care home managers stated that we need to be clear about how to classify people where, for example, they are not able to stand (so don't have a standing diastolic blood pressure reading), and we have clarified this in both trees. If one or both of these trees are useful, then we plan to work with primary care colleagues to develop a reporting protocol for blood pressure readings taken in care homes (so that worrying readings are reported back to the resident's GP), and we will also develop a training plan for staff (possibly using video to standardise the way that the questions are asked and tests carried out and interpreted). This part of the research will first check that one or both of the decision trees are diagnostically accurate enough to be useful.

Currently available evidence on dehydration in older people is patchy. It is vital for the health and wellbeing of older people, and to reduce unplanned emergency hospital admissions, that we identify dehydration in the community and residential care, and learn to prevent it. Our approach to develop the research base for water-loss dehydration is to assess the validity of these two short decision trees for use by care home staff. Validation is both essentialist (against the best reference standard of water-loss dehydration, serum osmolality), and consequentialist (assessing the utility of this panel in predicting mortality, functional status and QoL – using the data from the cohort element of the original DRIE study) (30). This will prepare for future randomised trials

of screening and intervention to prevent or redress impending water-loss dehydration on important health outcomes in older people. This part of the research is checking that the decision trees we created with care home residents are truly diagnostic.

Primary Aim:

The principal research objective is to test two short decision trees to assess whether either will usefully identify water-loss dehydration in frail older people.

Secondary aims:

Additional objectives include:

1. Assessing the acceptability and invasiveness of the individual assessments to older people living in residential care
2. To assess the relationship between nutritional status (assessed by change in weight over the past 6 months, body mass index, Mini Nutritional Assessment, Malnutrition Universal Screening Tool, haemoglobin) and hydration status in care home residents.
3. Assessing some additional promising clinical and/or physical signs or questions (such as assessing foot skin turgor, dry lips, asking participants whether they feel out of sorts, and whether they drink as much as they need to stay healthy, completing the mini-mental state exam, observing whether participants taste their drink immediately and recording their Barthel score and number of medications prescribed) so that if the current decision tree does not prove useful we have a strong evidence base (from 200 participants in the DRIE study, and a further 200 participants in DRIE 2) to allow development of a better decision tree.

Study design

This will be a cross-sectional study (researchers will be blind to reference standard results when assessing index tests). The design of the first DRIE study incorporated understanding gained from the current literature on dehydration, advice from members of Patients and Public In Research (PPIRes), discussions and debates with research mentors and the DRIE steering group, results from (and debates during development the protocol for) our current systematic review of diagnostic accuracy of clinical and physical signs of water-loss dehydration in older people (which includes many current researchers in dehydration within the author group, and has now been submitted for publication (27;28;31)), advice from the NIHR Career Development Fellowship interview panel (who are funding this research) and our ethics committee, and discussions with care home managers and staff during the process of recruiting homes interested in participating in this research. For this study, DRIE 2, we additionally incorporate our learning during the carrying out of the original DRIE study, as well as advice from our advisory groups of care home residents and care home staff, and further advice from our steering group.

We will carry out primary research to assess the diagnostic accuracy of a promising decision tree. This tree was developed in a population of 200 care home residents, and will be assessed in another population of 200 care home residents, all different individuals (although some may live in the same care homes as DRIE participants). Serum osmolality will be the reference standard for water-loss dehydration (>300mOsm/kg implies current dehydration). As serum osmolality is not commonly available in residential care, a simple decision tree of tests to be carried out by care home staff could be used regularly to assess residents for dehydration.

Sample size: we will recruit 200 participants. This was the power calculation for the first DRIE study, which proved appropriate: Using the Kappa statistic as a measure of diagnostic accuracy and assuming a dehydration prevalence (current or pending categorised together) of approximately 40%, a sample size of 180 would ensure a standard error of no more than 0.05 for

Kappa values (between a decision tree and the reference standard) in excess of 0.75. 200 participants recruited would allow for 10% to terminate assessment before all signs are assessed or to provide unreadable blood samples. For values of at least 0.6, the standard error would be no more than 0.06. Thus, this sample size should provide an estimate of diagnostic accuracy with a precision to allow an assessment of the practical utility of the identified signs. This proved highly appropriate for the first study, and of 200 interviews, we had useable data on serum osmolality for 188 people, on whom we based our analyses.

Inclusion criteria: People aged 65+ living in residential care (care homes, nursing homes and mixed homes) in Norfolk or Suffolk.

We will include participants regardless of their capacity to provide informed consent, although the study is designed to protect all participants and include them only if they find the research acceptable. Inclusion of those with dementia was strongly encouraged by the NIHR interview panel that awarded the funding for this research, as those with dementia are at greatly increased risk of dehydration, so it is vital that the tool developed is applicable to those with dementia as well as those without. This decision has been strongly supported by care home managers and staff before and during the course of the original DRIE study. We will only include adults who can provide their own informed and signed consent OR whose consultee has provided signed consent that they believe that the resident would have consented if they were able to make the decision themselves.

We do not plan to stratify inclusion by age group (as most of those living in residential care will be either physically or mentally frail, all will be at some increased risk of dehydration), or by gender (although the samples are likely to be weighted towards women, as more care home residents are women). While we are aiming for a representative sample of care home residents, we will not exclude any interested participants on this basis. Our sample of care home residents is likely to be rather less frail than the average resident as those with better physical and cognitive capacities are more likely to feel able to participate, but we will collect a small amount of data on all residents in the homes we work in to assess the representativeness of our study sample.

Exclusion criteria: we will exclude those who the care home manager is aware have been diagnosed with renal failure or heart failure, as fluid physiology changes with these conditions (and fluid retention is more likely). Those in receipt of palliative care, or with illnesses that suggest they are unlikely to survive for at least 3 months will not be recruited. Additionally we will not seek to recruit people who are unable to provide their own consent, and are known to be frightened of, or upset by, needles or blood tests as we will assume that the process of the interview and blood sample will be upsetting to them.

Recruitment: the chief investigator (CI) and/or research assistant (RA) will contact care home managers in Norfolk (NOT residents or relatives) to discuss the participation of the care home in DRIE 2. Contact will have been made through letters sent to care homes, followed by phone calls to arrange a visit by the CI or RA. Care home managers will be given a pack of information on the DRIE 2 study, will be asked to read the Participant Information Sheet (*Participant Info Sheet DRIE2 6 April 14 v1.0*), and to sign the Gatekeeper Consent Form (*Gatekeeper consent 6April14 v1.0*). Following the home's decision to participate we will agree date(s) for open meetings with residents, relatives and staff, and the home will be sent posters to display about the meetings (*Poster for dehydration research DRIE2 6April14 v1.0*), as well as letters for each resident, relative and staff member (in envelopes, to be addressed by the home), inviting them to the meetings. The envelopes will include the letter (*Residents relatives staff invitation general DRIE2 6April14 v1.0*) and the Introductory Leaflet (*Introductory Leaflet for Residents Relatives Staff 6April14*

v1.0). In some cases individual letters may be replaced by information and the leaflet enclosed in a home newsletter, as appropriate.

Older people living in care homes are potentially liable to undue persuasion to participate, but this will be carefully avoided regardless of capacity to consent. We will offer time and opportunity for potential participants to discuss their participation (or lack of it) with ourselves, their relatives, care home staff and management, ensuring that they understand that participation is totally voluntary and that no loss of care or support will result from a decision not to participate. They also need to know that if they participate there will be a blood test and that this may cause some pain and has the potential to cause some bruising or bleeding (though this will be minimised).

We will be including some participants who are able to give their own informed consent, and some who are unable to consent on their own behalf. The principles behind this process (described below) are that if a resident can give their own consent (or decline consent) then this will be accepted regardless of the opinions of relatives. However, if a resident is unable to consent on their own behalf, but appears interested in taking part, we will ask the responsible consultee to consider providing consent on behalf of the resident on the basis that they feel the study is useful and appropriate, and that they believe that the resident would give their own consent to participation if they were able to do so. Any participant may withdraw consent, without providing reasons, at any point – verbally or through their behaviour.

Recruitment of participants (residents) will occur in several stages. For each home:

Visit 1. A researcher will visit the home, having sent invitations to staff, residents and relatives (individually or via a newsletter), to discuss the study with staff (we may need several meetings to include different shifts), relatives (we will offer a time during the day and an evening meeting time if the care home manager feels this is appropriate) and residents (as appropriate within the home, we may speak to small groups of residents, or residents individually, after introduction by home staff). We will not recruit on this day, but encourage interested residents to discuss the study with their friends, relatives and staff. Further copies of the Introductory Leaflet (*Introductory Leaflet for Residents Relatives Staff 6April14 v1.0*) will be provided to anyone who would like one.

On this day we will also ask the home manager to complete a list of residents (not named, but coded by room number) with their age, gender, months living at the home, weight, height and MUST score. For each resident we will also ask them to indicate any reasons for not including the resident – residents will be excluded if they are aged <65, have diagnosed heart failure or renal failure or have a short life expectancy. Care home managers may also exclude residents who they feel would be upset by our visit, or who are too ill. We will also exclude any residents who participated in the original DRIE study. For residents whom the home believes fulfil our inclusion criteria we ask that they provide the residents name so that we can ask the resident personally whether they would like to participate in DRIE 2. This list will be collected on the day of visit 2 (see *Recruitment Inclusion List for Care Homes DRIE2 6April14 v1.0*). This provides the study with anonymous data on the full care home population (to allow assessment of how typical our participants are) without collecting data that would impinge on the rights of those who decline to participate or who are not eligible.

Visit 2 (approximately 1 week after visit 1). Following an introduction by care home staff, we will ask the residents named on the list provided by the manager individually (as being appropriate to approach and be included) whether they would be interested in participating in the study (having repeated the basic information on the study as many may not remember clearly). We will briefly describe the study using a participant information leaflet with large print and

pictures to help depict it clearly (*Participant Info Sheet DRIE2 6April14 v1.0*). The potential participant will retain the leaflet.

1. If the participant seems interested in participating we will ask them some questions (see the first page of *Capacity Assessment and Informed Consent, own consent DRIE2 6April14 v1.0*). Being able to answer suggests that they have capacity to give their own consent as they are able to retain information long enough to make an effective decision, are capable of making this decision at this time, and are able to make a free choice. As part of this we will ask the resident to tell us
    a. what the study is trying to do ("can you tell us what the study is about?" - expected answer is anything to do with drinking or hydration, which indicates that they understand the purpose of the research),
    b. what they will be asked to do with us ("if you take part in the study, what will happen to you?" - expected answer is to have a blood test, to answer some questions and have some simple physical tests, suggesting that they understand the nature of the research, and the potential burden and risks),
    c. who will know the results of the blood and urine tests, and blood pressure ("If you take part in the study, who will we tell the results of the blood & urine & BP tests to?" - expected answer is that care home manager and their GP will be told the results, indicating understanding of the nature of the research and how their information will be used, as well as understanding a potential benefit of the research),
    d. Whether they mind if we ask the care home manager about their health, wellbeing and medications ("if you take part in this study may we ask [the care home manager] about your health, wellbeing and medications?" - expected answer would be yes, indicating consent to use their current health information now and also their live status as outcome data even though they will not be able to give consent at that time if they have died), and
    e. Whether they know what will happen if they don't participate ("if you decide not to take part in this study, will it cause any problems?" - expected answer that there would be no consequences, their care and support would not alter, showing that they understand that participation is entirely voluntary).
2. If residents can tell us these crucial bits of information about the study we will accept that they have capacity to provide their own informed consent. If they also choose to be involved we will ask them to sign the consent form (see the second page of *Capacity Assessment and Informed Consent, own consent DRIE2 6April14 v1.0*). This form will also be signed by the researcher.
   If the resident is not able to answer the above questions but has expressed a desire to be involved, then we will ask the care home manager if they believe the resident to find blood tests frightening or upsetting. If so, we will not try to encourage participation any further. If not, we will send the consultee a letter asking for consent for the resident to participate (*Letter to Consultee – please advise DRIE 2 6April14 v1.0*). The consultees advice will be based on the consultee feeling that the research is worthwhile, and also that they believe that the resident would have wanted to participate in the study if they were still able to make the decision for themselves. Under the Mental Capacity Act 2005[1] a "personal consultee" means "a person who is engaged in caring for the participant (not professionally or for payment) or is interested in his/her welfare, and is prepared to be consulted. If no appropriate person can be identified who is willing to act as a personal consultee, the researcher may consult a "nominated consultee", i.e. a person independent of the project appointed in accordance with the Department of Health's Guidance on nominating a consultee for research involving adults

[1] For more information on capacity and consultees see http://www.hra.nhs.uk/resources/research-legislation-and-governance/questions-and-answers-mental-capacity-act-2005/

who lack capacity to consent. The consultee advises the researcher on what the participant's wishes and feelings would be if they were able to consent for themselves, and on whether they should take part. The consultee does not give consent, only advice. That advice will be respected.

Visit 3 (approximately 2 weeks after visit 2, may take place over several days). At this meeting we will sit with each resident for whom we have consent (their own or via a relative or consultee). We will briefly describe the study again (with pictures, using the Participant Information Sheet), check that they are happy to participate at this point and then move into the research interview. If at any point the resident decides not to participate, or appears uncomfortable or upset, or moves away then we will assume that consent has been withdrawn, whether or not the resident is able to express this verbally. For those residents for whom consent has been provided by a relative we will try again once more at a different time of day (or a different day) when their mood may have altered, but again, only proceed if the resident appears happy to work with us. We will not try a third time.

Some residents may want their consultee or a member of care home staff with them during the interview. In this case we will aim still to gather answers to all our questions from the resident (participant) rather than the consultee or member of staff. If this proves impossible questions that are answered by anyone other than the resident will be labelled as being answered by their surrogate (with a star).

As the blood test is likely to be the point at which residents decide to withdraw, and also which may lead residents to worry, this will occur 5-10 minutes into the research interview (once formalities have been completed and the resident relaxed in a sitting position) – this will waste less of the residents time if they decide not to have the blood test, and mean that they don't worry about the looming blood test through the remainder of the interview. It also allows us time to keep pressure on the wound and ensure bleeding has ceased, while working through some of the interview questions and tests. If the first attempt at venepuncture fails then we will relax the participant, progress with the interview, then allow one more attempt at venepuncture. If this second attempt succeeds (in that enough blood is collected for assessment of serum osmolality) then data collection will progress as planned, but if it fails the interview will be abandoned (as the remaining data are not interpretable in the absence of serum osmolality readings). Blood for assessment of serum osmolality will always be collected first (before other blood samples) so that if only one reading can be carried out on the blood samples it will be serum osmolality.

Methodology

In detail, we will collect only data needed to carry out the research aims. All data collection will be by Lee Hooper (CI) or Diane Bunn (RA) or both. The three data collection forms include that used to gather data from the care home about a resident who is participating in DRIE2 (*1 CH re resident data collection form DRIE2 6April14 v1.0*), that used during the face-to-face interview with the participant (*2 resident data collection form DRIE2 6April14 v1.0*), and that used once with each care home to collect information on the care home itself (*3 CH general data collection form DRIE2 6April14 v1.0*).

Resident identification and to allow blood test results to be provided to the care home manager and GP (retained in a separate table within the access database so that the dataset can be easily anonymised at any point by removing this table):

- Resident number
- Resident full name

- Likes to be addressed as
- Resident date of birth
- Care home number
- GP name and address
- NHS number

Within the main electronic dataset we will collect:

- Resident number
- Resident age
- Gender

Reference standard data: serum osmolality, serum sodium, serum potassium, serum glucose (random) and serum urea, serum creatinine, liver function tests.

- Blood samples will be identified by study number, date and study name, date of birth and gender, and analysed at the Norfolk and Norwich University Trust Pathology laboratory (all samples will be delivered to the laboratory within 4 hours)
- Results will be returned to the CI
- Serum osmolality information will be interpreted and provided to the care home manager (or deputy) and the resident's general practitioner
- Blood samples will be destroyed after analysis within the laboratory
- We will request the following blood tests for each participant:
    - Serum osmolality (directly measured by freezing point depression)
    - Urea and electrolytes (U/Es), including bicarbonate
    - Liver function tests (LFTs)
    - Random blood glucose

Index tests (to use as described in the standard operating procedures of DRIE 2). The flow of the tests and questions will be roughly as follows (see *2 resident data collection form DRIE2 6April14 v1.0,* but we will adapt this to improve the way that the testing works as necessary):

1. Start by moving to an appropriate location, ideally the resident's own bedroom, and ensuring that if they would like a care worker or family member with them that this has been organised (and that if they do not want anyone with them this is also ensured).
2. Resident is settled in a comfortable seat. During this time to have a general friendly chat as appropriate with the participant. Once settled to ask short questions about how the resident's occupation, education, marital status, whether they are feeling out of sorts, whether they have pain in their bladder or leak urine, whether they always drink as much as they would like to and drink first thing in the morning and at lunch time.
3. Take blood samples (once resident has been sitting for 5- 10 minutes to ensure standardisation), using needle and syringe, as taught by the Norfolk and Norwich University Hospital Phlebotomy department. Label and store all samples, dispose of all sharps as per SOP.
4. With resident still sitting conduct physical exams, assessing lip dryness, dryness of inside lower lip, skin turgor in back of hand and foot, crinkliness of skin on lower and upper inner arm, and ulnar length.
5. Conduct Mini-Mental State Exam (MMSE (32;33))
6. Once participant has been sitting comfortably for at least 10 minutes measure blood pressure:
    - Assess blood pressure and pulse rate while sitting.
    - Help resident to stand in front of stable chair (using usual aids, help support them in case of dizziness), then measure BP after standing for 1 minute and 3 minutes. After the 1 minute measure ask if they feel dizzy or bad in any way (help them to a sitting position if any problems)

- While standing assess whether breathing is normal, deep or deep and rapid
- Ask whether the resident would mind if the care home staff assessed their sitting and standing blood pressures every few weeks

7. Ask the participants thoughts about the interview, whether they would find any of the tests annoying, painful or onerous if performed by care home staff every few weeks and ask them their ethnicity
8. Ask the participant for a urine sample – help them to toilet (if help is needed), ask for a urine sample (collected in disposable "hat" in toilet). Help participant back to their preferred location in the home, make them comfortable with a drink and snack (where appropriate). Return to test urine:
   - Urine colour (against standard chart) and volume
   - Urine specific gravity (using dipstix), other dipstix measures
   - Urine specific gravity using refractometer
   - Urine volume (mls)
9. Help the resident back to their normal chair or position in the care home, and offer them a drink (or get the care staff to offer them a drink). Observe this process, including whether the participant tastes the drink immediately.

To ask of care home manager for each participating resident (see *1 CH re resident data collection form DRIE2 6April14 v1.0*)**:**

- Pre-interview check of exclusion criteria and blood test risks (including whether the participant has HIV or hepatitis, is on warfarin or steroids, their level of continence and whether either arm is unsuitable for taking blood or measuring blood pressure).
- Information on participant risk of dehydration, need for thickened drinks, whether the participant needs help to drink, equipment needed for drinking and questions relating to the Mini Nutritional Assessment (including recent reduction in food intake, psychological stress or acute disease, and mobility level)
- History of recent (over past week) vomiting, diarrhoea, cold, urinary tract infection (UTI) and/or fever
- Whether the participant appears well, out of sorts or ill today
- History of recent (over past 2 months) hospital admissions and/or healthcare professional contact
- Current and chronic illness (including diabetes, constipation, delirium, dementia and depression which can increase the risk of dehydration)
- Functional status assessment (Barthel Index, well validated, covers crucial areas of functional status for care homes, fast (34;35))
- Current medications (and doses)
- Weight history and height

Care home data (also to ask of care home manager, but once per home at baseline, see *3 CH general data collection form DRIE2 6April14 v1.0*):

- Care home manager and contact details
- Total number of residents currently, number diagnosed with dementia, number with dementia (diagnosed or not) and type of care offered (residential/ nursing/ dementia etc)
- Whether any member of staff has a specific role around dehydration
- Measures the home takes to prevent dehydration in residents
- Presence or not of en-suite toilets
- Number of staff in several categories

Data analysis: Data will be entered into an access database to be stored, cleaned and analysed. Assessment of water-loss dehydration will be on the basis of serum osmolality, a binary variable (i.e. euhydrated or currently dehydrated, cut-off at 300mOsm/kg). Initial analysis will assess the

diagnostic accuracy of decision trees 1 and 2. This is the main analysis and we believe that one of the decision trees will prove useful. If one of the trees is useful (minimum sensitivity 75%, minimum specificity 60%), then we will publicise the better decision tree and train our care homes to use it. If neither decision tree is useful enough as a diagnostic tool then the additional data gathered on diagnostic accuracy of individual tests in DRIE 2 will be added to the data on the same tests from DRIE, assessed as individual tests and used to develop further combined diagnostic tools (using logistic regression and 'Classification and Regression Trees' (CART (36)). Papers written will conform with STARD reporting standards for diagnostic studies (37).

Position of this study in the 3-year funded research plan

This study is part (section 5 below) of a 3-year NIHR funded research (as a Career Development Fellowship, also including considerable training) which aims to improve the health and wellbeing of older people living in the community through:

1. Systematic review (and summary) of research on prevention and reversal of impending water-loss dehydration, making best evidence accessible to UK health and social care workers,
2. Primary research to identify a simple decision tree of dehydration signs in residential care so that prevention and treatment strategies can be rapidly mobilised,
3. Clarifying associations between dehydration and health, functional status and quality of life in frail older adults,
4. Development and dissemination of an evidence-based statement of appropriate action to be taken when dehydration is identified in older people living in care homes to improve hydration in older people, and
5. A pilot study of the developed dehydration tool (decision tree of clinical signs) to assess its practicality, invasiveness, acceptability, and diagnostic accuracy in a different context,
6. The 3 years will be informed by an expert group of older people living in residential care and care staff, and will result in high quality publications as well as development of expertise, research capacity, collaboration networks and dissemination strategies to ensure future research & health improvements for frail older people.
7. The RA will also plan, develop and carry out a small piece of independent research as part of their PhD work.

	2012				2013				2014				2015	
	J-M	A-J	J-S	O-D	J-M	A-J	J-S	O-D	Jan-Mar	Apr-Jun	Jul-Sept	Oct-Dec	Jan-Mar	Apr-Jun
Expert group meetings, 6														
Systematic reviews (SR), 1														
SR write up & dissem, 1														
Ethics for primary studies	2,3			7	7				5	5				
Cohort recruitment & data collection, 2														
Cohort follow up, 1&2 yrs, 3					1yr	1yr	1yr	1yr	1,2y	2y	2y	2y	2y	2y
Primary analysis-decision tree, 2														
Consensus statement, 4														
Cohort secondary analysis, write up & dissemination, 3														
Pilot of dehydration tool, 5														
RA's PhD project work, 7														
Capacity & network dvpt, 6														

Safety considerations

The risks of participation in the research to residents centre on the blood sample as other tests are simple and non-invasive. The risk from the blood sample includes pain, bruising, infection and excessive bleeding. These risks will be explained to the residents, and the risks minimised by using correct technique (including washing hands, using an alcohol swab), supporting the arm used, using a tourniquet correctly, collecting all materials before the venepuncture is begun, covering the puncture site and applying pressure for 3 minutes after needle withdrawal, check for haematoma and apply an adhesive bandage. Samples will be pre-labelled and transported within a labelled biohazard transport bag, needles disposed of in a sharps box and all other materials discarded appropriately. (For training in phlebotomy see quality assurance section).

There is greater risk of excessive bleeding for those residents on warfarin treatment, so any residents on warfarin will be identified before their interview, and pressure maintained on the puncture for longer, with especial care to ensure bleeding has ceased before the end of the interview. Samples from any residents with HIV or infectious hepatitis will be labelled "Risk of infection".

Balance may be an issue for some residents, so we will collect urine specimens by asking the resident or their carer to place a sterile "hat" within the toilet, rather than needing to hold a container while passing urine. When we ask residents to stand to assess postural changes in blood pressure (orthostatic hypotension) we will encourage them to use any equipment that they would usually use to help with standing and walking, and will also stand with them in physical contact, and provide any necessary support for the 3 minutes of standing. They will stand in front of a solid chair, and so if any resident becomes dizzy or needs to sit down they will be immediately helped back into a safe sitting position.

Additional burdens to participants include the time taken for the interview and anxiety before the blood sample or other tests. In order to ensure that the resident is not anxious we will aim to be friendly and speak quietly with the resident (not between researchers or with care staff) about the resident's family or history or previous job or where they lived before coming to the care home, to help distract them. If the resident is too anxious we will suggest that we discontinue the interview without taking blood. We will try to make the process of the interview interesting and enjoyable, but will allow residents to leave and discontinue if or when they want to.

Benefits to residents include a small token of gratitude (a £10 voucher OR an equivalent value token felt appropriate by the care home, such as attractive mugs or cups) for all residents who complete the interview (with a blood test and all relevant clinical and physical tests OR where we try but are unable to take blood from the resident). We hope that residents will also enjoy their time with the researchers.

The results of all blood and urine tests, and blood pressure, including the blood test on serum osmolality (giving a definitive assessment of whether the resident is hydrated, or has impending or current dehydration) will be provided to the care home manager and the residents GP, helping to optimise their care. This will be the first planned contact of the study with the participant's GP, we will not be pre-notifying GPs of participation in the study. There are three letters for GPs and managers with participant results, one for participants with normal hydration (*letter to manager & GP osmolal normal DRIE2 6April14*), impending dehydration (*letter to manager & GP impending dehydration DRIE2 6April14*) and current dehydration (*letter to manager & GP current dehydration DRIE2 6April14*).

Where the pathology laboratory is concerned about any of the blood test results they will phone through results to the consultant who requested the blood test. When this occurs (the lab has Lee's and Diane's mobile numbers to facilitate this, as we will have requested the tests) we will

phone on the urgent results to both the resident's GP and their care home within 24 hours (much sooner where feasible), following this with the usual letter including all the relevant results.

If the researchers come across any important information such as suspicion of elder abuse such information will be reported to the care home manager, and also to Norfolk Adult Social Services (or the local Adult Social Services team for care homes outside Norfolk).

Quality assurance

Delivery of all the tests will be practiced and standardised by Lee Hooper (CI) and Diane Bunn (RA) so that they flow well, some can be carried out concurrently where this is safe and effective use of time. The researchers have already developed standard operating procedures for each test, but before starting the second study they will ensure that the results are reproducible between the 2 researchers. They will carry the tests out on several advisory group members (who are happy for us to do this), according to the Standard Operating procedures (SOP) for DRIE. The SOP will be rewritten and printed so it is specific for DRIE 2 (including the correct tests in the correct order) before data collection begins, and will be learnt by the 2 researchers referring frequently back to the standard operating procedures. We will check reproducibility of assessment using kappa statistics (aiming for a kappa of >0.7 for every test) before carrying out any of the tests within the study (to ensure all data are high quality and useful, and we do not waste any participant data).

Lee Hooper and Diane Bunn are both trained in phlebotomy. Diane Bunn is a registered nurse and has been taking blood samples for more than 20 years in clinical and research contexts. Lee Hooper was trained in phlebotomy on the Norfolk and Norwich hospital standard 12-hour training package (using the equipment we will be using in care homes), before and during the original DRIE study. Lee gained additional supervised on-ward experience with older patients, and her trainers tested her to ensure that she was appropriately skilled to take blood samples in care homes. This training was supervised and assessed by Gillian Blythe, Phlebotomy Manager at the Norfolk and Norwich University Hospital. Both Lee and Diane will undergo a "refresher" training with Gillian Blythe to ensure they are using appropriate and up to date local methods before the start of DRIE 2.

Blood samples will be delivered to the Department of Laboratory Medicine, Norfolk and Norwich University Hospitals Trust (Norfolk, UK), within four hours of collection, and samples analysed immediately. The laboratory is fully accredited with Clinical Pathology Accreditation (UK) Ltd., has daily internal quality control run along with calibrators and fortnightly they are judged against their peers (external quality control). Serum osmolality will be measured by assessment of depression of freezing point using the Advance Instruments Model 2020. Osmometry measures the total molar concentration of dissolved solids in any solution. The freezing point of a solution is depressed in direct relation to the amount of solute in solution. This model has a repeatability of ±3 mOsm/kg (1 SD) in the 0 to 400 mOsm region and linearity of ±3 mOsm/kg with drift of less than 1 mOsm/kg H_2O per month. Serum osmolality has appropriate levels of analytic variation and an area under the curve of 0.95 (for a cut-off of 297 mOsm/kg, with sensitivity of 90% and specificity of 100% in young adults dehydrated via exercise in a hot environment and losing 2-7% of their body weight), making it a useful marker of water-loss dehydration when tested on a single occasion (38).

Dissemination of results

We will develop and disseminate an evidence-based consensus statement of appropriate action to be taken when dehydration is identified in older people living in care homes. Lee and Diane are working with others interested in dehydration research and practice through NHS England and the Cross Parliamentary Party Hydration Forum (lead by Baroness Greengross) – these are excellent fora from which to disseminate and prioritise our findings. We are working within these groups to develop a consensus statement on assessment of dehydration in care homes, and a dissemination plan.

Dissemination is likely to include publication in at least one high quality scientific journal, and writing up the research and guidelines to be accessible to older people, care home staff and members of the public (to consider open access journals, websites, paper and DVD dissemination). We will put the dissemination plan into practice, using our developed collaborations and potential conference presentations. We will present data at the British Society of Gerontology conference, Nutrition Society Summer meeting, an INVOLVE conference and the American Dietetic Association Conference.

We currently produce a DRIE newsletter 3-monthly, that is sent to all involved care homes, and to all individual study participants. The newsletters are all available on the DRIE website, and aim to keep the care homes and participants interested and involved, and we are beginning to let participants and homes know the early results of the DRIE study. We will continue to do this and will include homes and participants for DRIE 2 in the distribution list, until the main results from both studies are known and disseminated. We will also maintain the study website (http://driestudy.appspot.com/) which provides information to those who wish to find out more about the study (it will allow access to DRIE 2 participant information sheets, researcher and sponsor contact details, the newsletters and summarise and signpost presentations and publications).

Problems anticipated

The recruitment procedure will be time consuming and slow, but we have learnt a great deal in the original DRIE study, which we will operationalise to recruit to DRIE 2. We will ask care homes participating in the original DRIE study whether they have any new residents who may like to take part in DRIE 2 – this will be time and cost-effective as we have built up good relationships with many care homes, and will help to reinforce the message that drinking is important in these homes. We will also approach new care homes, to increase the numbers of our potential participants. The slightly complex procedures are necessary to ensure that residents have time and opportunity to discuss their participation with care staff and friends and relatives, which is very important in ensuring that consent is truly informed.

Procedures for recruiting those with dementia who are not competent to provide their own consent are slightly longwinded but again are important to ensure that only those for whom the study is appropriate become participants. We have tried these out in DRIE, and they work well. The issue of defining capacity to consent has been solved in a practical manner, by devising a core set of information that a participant needs to be conscious of before they are understood to retain capacity to consent. Those able to provide their own consent will do so, the consultees of those who cannot will be asked whether the resident would have chosen to participate if they were still able to make the decision.

Project management

Day to day management will be by the CI, Lee Hooper, with the aid of a detailed Gantt chart and protocol (progress will be formally discussed between Lee and Diane (RA) every fortnight with reference to the Gantt chart, which reflects the protocol).

The steering committee oversees our 3 year research work, and we will continue to use this committee to oversee DRIE 2. The steering committee meets every 6 months, requires an overview of progress and provides an opportunity to discuss and solve problems. The steering committee consists of the fellowship mentors, professors Lee Shepstone, John Potter and Paul Hunter, Professor Fiona Poland, who is the second PhD supervisor for Diane Bunn, Vicky Cowap (Quality Assurance manager at NorseCare, the group that now run care homes formerly owned and run by Norfolk County Council), Linda Gill of Age UK Norfolk, Joyce Groves, an elderly member of PPIRes (Patient and Public Involvement in Research), and Carol Free, a member of PPIRes who works in a Norfolk Care Home. Sue Steel, contracts manger, is also a member of the steering committee as the representative of the sponsor. The mentors are regularly available between meetings for support on specific practical, management and/or academic issues.

Lee Hooper (CI) will be the first port of call for queries about the study, but if any participants or care homes have worries about the research or its conduct they will be encouraged to contact Sue Steel to discuss them. Lee Hooper will have day-to-day control of the budgets and will review them monthly.

Ethics

Mental capacity issues

The 5 core principles of the Mental Capacity Act (39) are retained within this research proposal in that:

1. Each resident will be assumed to have capacity to make their own decision about whether to participate in the research unless we establish that they lack capacity
2. We will support each resident to make their own decision by explaining the research to them in simple terms, backing this up with clear pictures (and written material with large text), and asking short simple questions to enable the resident to demonstrate their capacity.
3. Any person who declines or agrees to participate and who has capacity to make that decision will have their decision honoured.
4. Participation of a resident in the research, when decided by a consultee, will be based on the known preferences of the resident for participation in this sort of research when they still had capacity to decide. There are potential benefits of participation, for those who are not unduly upset by having blood tests, in the added information to the care home manager and GP on their blood test results, including their hydration status. Thus the decision can be seen to be made in the best interests of the resident.
5. If we could appropriately assess dehydration status in a way that did not involve a blood test we would use that way, but there is no other good reference standard (see introductory discussions).

Additional to these principles, there are specific rules for research including those lacking capacity (40). We will not approach residents or relatives until ethical approval for the research has been attained. Approval will be accepted from the residents consultee only if they believe that that the resident would have wanted to participate in the research if they still had capacity. If at any time a resident is unhappy with participation in the research, expressing this verbally or physically (for

example, by leaving or seeming frightened or worried, or telling us to stop) then we will assume that consent has been withdrawn and the research stopped. As those with dementia can have mood swings, for residents without capacity we will try once again to carry out the research (at a different time, with a gap of at least 2 hours, when the resident appears alert but calm). However, if the resident expresses disinterest or unhappiness with the research at the second attempt, the research will cease and we will not try again, so consent will be assumed permanently withdrawn. This process will be recorded.

Confidentiality

All data collected within this study will be linked to a specific resident. As each resident is recruited we will randomly allocate them a unique 4-digit number. The consent form, and a single isolated table within the access database will link the number with the resident's name, date of birth, GP name and address and care home. The main access database tables will include only the number, not the resident's name, so that once the linking table is removed the electronic records on their own will not be traceable back to individual residents. However, each test or piece of information will still link with the individual's serum osmolality within the data set (as this is needed to develop the tool).

The only raw data that will be available to anyone other than the CI and RA will be the result of the blood and urine tests and their blood pressure, which will be provided, with the resident's name and date of birth, to the care home manager and the resident's GP only. The researcher and the research assistant will both understand that resident data is confidential, and will not be disclosed to anyone except in these circumstances.

All paper data will be stored in locked filing cabinets, within secure offices (restricted access to Norwich Medical School staff only). The electronic data will be password protected according to UEA/ GCP data protection policies.

One potential issue is that those who are confused may wish to have a familiar face with them during the interview, either a member of staff or a family member, and family members may wish to be present. We will aim to include staff or a family member in the interview where this is desired by the resident, but will express the need for confidentiality where a resident is not keen for another person to be present.

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