Study 1 Protocol: Adverse Drug Reactions among children admitted acutely to hospital

Study description

Document history

This protocol is based on version 1 of the protocol for Study 1 drawn up by Mark Turner on 6th July 2007 and amended on 26th September 2007 and 19th January 2008. It was revised in the light of a pilot study by Ruairi Gallagher on 28th May 2008.

1 Study description

1.1 Study design

Cohort study

1.2 Subject selection

Single site: Alder Hey Children's Hospital

1.3 *Inclusion criteria.*

The overall study population will be all children acutely admitted to hospital as an emergency. This will be emergency admissions either via the Emergency Department or directly to a Ward. The subgroup of interest, "cases", will be children with suspected ADRs after exposure to any systemic or topical medicinal product (including alternative remedies such as herbals and aromatherapy) at the time of admission or within the preceding two weeks. Suspected ADRs will be defined as those admissions which involve any event that study team consider could possibly be an adverse drug reaction.

1.4 Criteria for not recruiting children to the study.

Elective surgical and medical admissions, including elective day-case admissions.

Intentional/unintentional drug overdose.

Admission due to drug misuse (of prescribed and illicit drugs) by patient and/or parent.

1.5 Recruitment

Participants will be recruited on the basis of a data entry tool embedded in routine admissions processes. This data tool will be paper based and will capture identifying information, source of admission and the medication history. Admissions will be identified on a daily basis by use of downloads from the hospital computer system.

1.6 Monitoring of recruitment

Hospital computer systems will be queried to determine whether all admissions have been recruited.

1.7 Sample size

This is a sample of convenience. We expect c. 12,600 admissions during this year-long study. This compares with a sample size of 18,820 in a similar study among adults admitted to hospital. Some of these admissions will be for children with more than one admission during the study period.

1.8 Data collection

As per methods below.

1.9 Awareness raising:

1.9.1 Run in period

A comprehensive training and awareness-raising programme will commence one month before the start of the study. This programme will ensure that all staff who admit patients are educated in taking and recording a full drug history, indicate common ADRs and demonstrate the information required to identify novel ADRs. It will be provided within existing programmes and by personal contact with relevant professionals.

1.9.2 During the study

Ongoing reminders will include posters and messages on the hospital's electronic patient data management system.

1.10 Methods

1.10.1 During admission process (i.e. routine clinical care)

A medication for all eligible admissions will be taken by the admitting clinicians as admissions occur and will include:

1. Identify all children acutely admitted to AHCH.
2. Obtain drug history relating to the 2 weeks immediately prior to admission.
3. Document whether member of staff admitting the child suspects an ADR.

The medication histories obtained by the admitting teams will be verified after the first 2 weeks of the study and periodically thereafter. This verification process will be undertaken by the study team who will interview a sample of parents and the family GPs in order to determine whether medication histories taken by the admitting team are complete.

1.10.2 Daily review of admissions by study team

At least one member of the study team will review all admissions on the next working day (including Saturdays). This will include:

1. Find clinical records of all children acutely admitted to AHCH.
2. Double check on exclusions.
3. Explore whether a medication error was present and classify as to whether it was a therapeutic error, dispensing error or administration error.
4. Define whether suspected ADR is present.

4a) examine list of known ADRs compiled from BNF / eMC

4b) identify any suspected ADRs identified on the basis of the clinical picture by admitting staff or review by study team.

5. If suspected ADR is present, gather relevant information from clinical record.
6. If necessary seek supplementary information from family / hospital team / primary care team about children in whom a suspected ADR is present.

The process of identifying suspected ADRs will be verified by the senior investigators two weeks after the start of the study and periodically thereafter. This verification will involve a selection of admissions in the first 2 weeks of the study. Senior Investigators will review all relevant data in a manner that is blinded to the outcome of the conclusions reached by the study team. This verification process will involve a mixture of cases that the study team designate as suspected ADRs and those designated as not suspected ADRs.

1.10.3 Review of suspected ADRs

Review meetings will take place twice a week. Initially, at least one senior investigator will attend each of these meetings in order to provide education and guidance. As the study team become more experienced, the senior investigators will be less involved in these meetings, but will continue to attend periodically to ensure quality control.

An initial triage of suspected ADRs will be done by at least 2 members of the study team during the week of the admission. This will include:

1. Naranjo's algorithm to identify likelihood of ADR when clinical information is complete

If definite / probable / possible:

2. Hartwig scale of severity
3. Type A / B (predictable in the light of pharmacology / idiosyncratic)

4. Hallas scale of Avoidability (this will be a consensus decision)
5. Yellow card submitted to MHRA

Suspected ADRs will be evaluated in several steps**:**

Step 1: decision made by study team

Step 2: decision made by programme team

Step 3: decision made by external reviewers

At each step, the evaluation will result in one of three decisions:

Definite, probable or possible ADR

Unassessable

not an ADR

When the status of the suspected ADR is not clear, the next step will be invoked.

1.10.4 Communicate ADRs to responsible clinicians

Whenever a definite, probable or possible ADR is identified, the study team will report the ADR to the clinical team responsible for the child's admission using a proforma sent to the clinician's secretary. The responsible clinicians will decide on subsequent clinical actions.

If a clinician informs a family about an ADR, the study team will ask clinical teams to communicate to families about an associated research project and gain feedback on permission to approach them about it (i.e. the qualitative research study).

The study team will identify which families have been informed about the ADR and where appropriate will inform the qualitative research team.

1.10.5 Data about children affected by ADRs

Following discharge the following data will be collected from the clinical record by the study team for all children affected by a definite, probable or possible ADR:

1. Did ADR cause admission or was it incidental?
2. Length of stay
3. Duration of intensive care
4. Investigations related to the ADR
5. Need for follow-up

a. Secondary care

b. primary care

1.10.6 Data about children not affected by ADRs

For all children admitted during the study period the following data will be obtained from electronic records.

1. Length of stay

a. stratified by age +/- presentation

2. Duration of intensive care

1.10.7 Senior review of ADRs

As part of quality control, decisions about ADRs will be reviewed periodically by senior members of the programme team. This is in addition to the initial validation procedures described in sections 9.10.2 and 9.10.3 above. After the initial phase of the study, senior members of the programme team will review all ADR cases where there is discrepancy between causality scores between study team members.

A sample of 10% of admissions in which a suspected ADR was not found will be reviewed by a the study team and a senior investigator.

1.10.8 Data handling

The study team will have responsibility for: data collection, recording and quality acting under Standard Operating Procedures (SOP) in accord with the Data Protection Act.

Data will be stored securely on Trust and University servers with back-up procedures described in an SOP.

Data will be retained in perpetuity in light of the possibility that ADRs in children may have consequences in later life.

All identifiable data will be held on the Trust computer network.

1.11 Analysis

1. Clean data and archive it in preparation for development of screening tool
2. Further analysis will use two denominator values (total acute admissions; admissions exposed to medication) to give:

a) proportions of ADRs for each class of drugs

b) proportions of ADRs according to licensing status

c) proportion of ADRs deemed to result from drug interactions.

3. Tabulate numbers of medication errors (including therapeutic, dispensing and administration errors) according to total admissions, medication class and age of child

Statistical analysis will be by the chi-square test.

Demographic data of patients with and without ADRs will be summarised using the mean and standard deviation for normally distributed data, the median and inter quartile range for skewed data, together with 95% confidence intervals. Similar statistics will be prepared for ADRs that are incidental to hospital admission.

We will assess the number of yellow cards generated over the study period in comparison to yellow card reports for the previous 5 years (using data from MHRA) in order to provide an estimate of the degree of under-reporting.

1.12 Stopping / discontinuation rules

We do not anticipate the need for stopping or discontinuation rules. If circumstances change, the Programme Executive Group will consult the Programme Steering Committee.

2 Research Governance

Study organization: Alder Hey Children's Hospital, Liverpool, UK.

The study lead(s) will be: Prof R Smyth.

The programme management group will be: Prof R Smyth, Prof M Pirmohamed, Prof AT Nunn, Prof P Williamson, Dr Mark Turner and Dr M Peak and will meet monthly.

The study steering committee will comprise: Prof Sir A Breckenridge, Prof M Rieder, Prof D Ashby and Dr J Raine.

The study team are: Kim Bird, Jennifer Mason, and Dr Ruairi Gallagher and will report to the Programme Executive Group each month.

3 Ethical considerations.

This is an audit project, as confirmed by NRES (letter on file). This is a review of existing data held in routine clinical records. The aim of the study is to enhance existing services using information and approaches that have been used elsewhere.

4 Approvals

This study will be done in accord with approvals from Audit, Clinical Governance and the R&D Department at AHCH

5 Finance

Funded by National Institutes of Health Research through a Programme Grant in Applied Health Research to the Investigators and administered by the R&D Department at RLC

6 Indemnity

Standard NHS provisions

7 Reporting and dissemination

Results of this study will be:

- reported to Trust bodies regularly (e.g. General Paediatric Forum)
- presented at regional meetings
- submitted to MHRA
- submitted for publication by peer-reviewed journals.

Study 2 Protocol: Adverse Drug Reactions among paediatric inpatients

1. Background

Alder Hey Children's NHS Foundation Trust treats 200,000 children a year from the North West of England, North Wales, Shropshire and the Isle of Man. The Accident and Emergency department treats 65,000 children every year. There are 309 in-patient and day case beds. During 2008 there were 33,905 in-patient episodes. This includes emergency admissions, elective admissions and day-case attendances. On an average day Alder Hey Hospital treats 167 patients in the Accident & Emergency Department, admits 121 patients, and cares for 230 In-patients.

For the period 1st January 2008 – 31st December 2008 the number of patients whose stay was longer than 48 hours was 7137.

In this study, we will use the definition of Edwards and Aronson. An ADR is "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dose regimen, or withdrawal of the product."

2 Study Objectives

1. To determine the incidence of ADRs in a paediatric inpatient population.
2. To characterise those ADRs identified in terms of type, causality, avoidability, severity, management required, duration and contribution to prolonged hospitalisation

3 Study Description

3.1 Study Design

A prospective cohort study carried out over 1 year.

3.2 Study Setting

Single Centre: Alder Hey Children's NHS Foundation Trust

3.3 Study Population

Children aged 0-16 years, who are inpatients for more than 48 hours.

3.3.1 Definition of ADR cases

ADR Cases will be deemed children with suspected ADRs to any systemic or topical medicinal product occurring during their inpatient stay whilst they are on a ward. This will include medication administered in the A&E Department.

If the same suspected reaction to the same medication occurs in the same patient on several occasions during a single inpatient stay this will be recorded as one ADR episode.

If the same suspected reaction to the same medication occurs in the same patient on a subsequent admission, this will be recorded as a new episode. A reference to the previous and subsequent admissions will be made respectively.

3.3.2 Inclusion Criteria Patients

Any child admitted to the hospital after the start of the study who then remains an inpatient for more than 48 hours will be reviewed.

3.3.3 Exclusion criteria Patients and Rationale

a) All patients in the transitional care unit

These patients are classified as inpatients on the hospital records system. They all have complex medical and nursing needs but are clinically stable. In general, they are awaiting transfer home or to a placement in the community. If they become acutely unwell they will be admitted for treatment to one of the wards included in this study.

b) All patients receiving medicines as part of their follow on treatment at home.

These patients are classified as inpatients on the hospital records system. They are receiving treatment at home from the community nursing team. The study team will not be able to make a daily review of these patients and so will not be able to fully assess any suspected ADRs.

c) All patients treated on the paediatric intensive care unit (PICU)

These patients are classified as inpatients in the hospital record system. They are managed with a high level of medical and nursing expertise. The proposed methodology does not cover all aspects of the clinical complexity and expertise required in an intensive care environment. The study team will therefore not be able to fully assess suspected ADRs. Patients who are inpatients before and/or after their PICU stay will be included

3.3.4 Inclusion and Exclusion Criteria Medication and Rationale

a) Prescribing or administration error

Excluded are all reactions which occur as a consequence of a prescribing or administration error including administration of a medication to a patient with a known allergy to this medication.

Rationale: These are adverse drug events resulting from medication errors.

b) Accidental ingestion of medication or deliberate medication overdose

Excluded are all reactions which occur as a consequence of an
accidental ingestion of medication or deliberate self-harm.

Rationale: These are adverse drug events resulting from medication errors.

c) Suspected reactions to total parenteral nutrition (TPN)

Excluded are reactions to TPN.

Included are reactions to any medicines added to TPN.

Rationale: The anticipated reactions to TPN include electrolyte imbalances which are difficult to assess for causality in complex patients. When prescribing TPN, clinicians assess electrolyte imbalances and amend the prescription in anticipation of, or response to these. The individualised nature of TPN prescribing means that a large amount of detailed data would need be collected for every patient receiving TPN.

d) Suspected reactions to intravenous hydration fluids

Excluded are reactions to intravenous hydration fluids.

Included are reactions to any medicines added to intravenous fluids.

Rationale: Similar to TPN.

e) Suspected reactions to medicines administered in theatre or in the department of radiology

Excluded are suspected reactions occurring whilst the patient is in theatre (including recovery) or in the department of radiology.

Included are suspected reactions to medicines administered in these departments which become apparent after the patient's return to a ward.

Rationale: Reactions which resolve quickly or which are considered to be expected or minor are not consistently recorded in these settings. It is therefore not possible to capture

information on all suspected ADRs using the proposed methodology. Suspected ADRs occurring on a ward will be picked up by the study team using the proposed methodology.

f) Suspected reactions to certain blood products

Suspected reactions to the following products are

Excluded:

- Red cells
- Platelets
- Cryoprecipitate
- Albumin solutions
- Fresh Frozen Plasma

Rationale: These products are not medicines. They are obtained from the transfusion service.

Included:

- Antithrombin III Concentrate
- Dried Prothrombin Complex
- Drotrecogin Alfa (activated)
- Factor VIIa (recombinant)
- Factor VIII Fraction, dried
- Factor VIII Inhibitor By-passing Fraction
- Factor IX Fraction, Dried
- Factor XIII Fraction, Dried
- Protein C Concentrate

Rationale: These products are listed in the BNF and some are under intensive surveillance by the MHRA

g) Suspected reactions to oxygen treatment

Excluded are reactions to oxygen therapy.

Rationale: Oxygen is not prescribed on the regular medication prescription charts. It will be difficult to obtain and record data of the amount of oxygen administered.

3.4 Sample size

This is a sample of convenience. We are expecting approximately 7000 patients to meet our criteria of having an inpatient stay lasting more than 48 hours during this year-long study. Some of these inpatient episodes will be for children with more than one episode during the study period.

3.5 Recruitment

We will use the already established hospital database HCIS MEDITECH for the recruitment of patients to the study. Electronic files containing a list of all children in the study population who meet the inclusion criteria will be automatically generated every 12 hours. All patients in the study population who meet the inclusion criteria will thus be enrolled. For ethical considerations see below (7).

3.6 Data collection

As per methods below.

3.7 Awareness raising

3.7.1 Run in period

A training and awareness-raising programme will commence before the start of the study. The study team will present Study 2 at appropriate meetings e.g. grand round, ward managers' meetings, doctor's induction, pharmacy clinical forum.

3.7.2 During the study

Ongoing reminders will include posters, and messages on the hospital's electronic patient data management system, intranet and internal communications. The study team will also continue to present Study 2 at appropriate meetings e.g. grand round, ward managers' meetings, doctors induction, pharmacy clinical forum

4 Methods

4.1 Data to be collected for analysis

The following data will be recorded in the study database for all patients in the cohort, with or without ADR, and will be used for the analysis of this study.

- Age on admission
- Gender
- Admission type (surgical, medical or both)
- Clinical team (surgical, medical or both) for each day of stay
- Time spent outside the hospital as part of daytime leave, weekend leave or overnight leave for each day of the stay.
- Duration of PICU or HDU stay in days
- Total length of stay in days
- Medication History
- Name of medication and preparation with BNF code, license status, black triangle status and off label status
- Route of Administration
- Indication
- Date given
- Dose and number of times given per 24hr period if administered intermittently ; dose or concentration and rate if given continuously

During the child's stay and following discharge the following additional data will be collected for all children affected by a suspected ADR:

- Trigger to suspect ADR e.g. nursing notes, laboratory results, observations
- Description of ADR
- Measurements relevant to the identification and evaluation of the ADR e.g. radiology reports, laboratory results and observations
- Specific treatment for ADR
- Type A/B
- Serious as specified by MHRA
- Action taken with drug as specified by MHRA
- Severity (Modified Hartwig Scale of Severity; see Appendix 2)
- Outcome (recovered/recovering/continuing/death/unknown)

If the reaction is ongoing at time of discharge and the patient had no further documented hospital visits (admission, A&E attendances or clinic appointment) the outcome will be

unknown. If the patient had further documented visits and the reaction is not documented then, the outcome will be recorded as recovered

- Duration of the ADR if known

This will be recorded in days. A reaction lasting <24hrs = 1 day; 24-48hrs = 2 days, etc.

- Drug interaction

We will not highlight the summative effects in this section

We will highlight the following drug interaction types in this section

1) Pharmacodynamic reactions, e.g. loop diuretic and digoxin

2) Pharmacokinetic reactions i.e. reactions affecting absorption, distribution, metabolism or elimination.

- Whether the ADR prolonged the admission and by how long
- Whether the ADR influenced the level of care (Admission to HDU cause or co-factor; Admission to PICU cause or co-factor) and if so by how long. This information will usually be readily available from the medical notes. In all other cases this will be discussed with the clinician. It will be documented whether clinician was contacted or not.

4.2 Data recorded in the study database but not used for analysis

Some data entered into the study database will be required for purposes other than analysis of the study, namely:

1) To identify each patient in the study cohort during and after the study. and to distinguish between multiple admissions for the same patient. Examples of these data would include patient name, hospital and account number.

2) To facilitate the daily review process and aid communication between members of the study team. Examples of these data would include past medical history and r**eason for admission.**

4.3 Data Sources

a) Personal details, admission and discharge details

These are routinely recorded in the hospital database HCIS Meditech.

b) Medical notes

These are recorded on paper and filed in the case notes.

c) Nursing notes

These are usually recorded electronically in the hospital database HCIS Meditech. For certain conditions or procedures designated patient care pathways combine both medical and nursing notes. These are paper records and will be available in the case notes.

d) Laboratory results

Details of all laboratory samples taken at Alder Hey and sent for analysis are available in the hospital database. Most reports will also be available in the hospital database. In all other cases a paper copy of the report will be available in the case notes.

e) Imaging results

Details and reports of all imaging results taken are available in the hospital database. The exception is any imaging undertaken in theatre where a formal radiological report is not available, for example cardiac catheter investigations and central line placements.

f) Observation and other charts

Observation charts including PICU charts, fluid balance charts, pain control charts and withdrawal charts are paper records which are usually kept separately from the medical notes. After discharge, these are filed together with the medical notes.

g) Prescription charts

As for observation charts.

4.4 Timing of data collection:

Data will be collected and entered into the database on a daily basis.

Baseline data will be collected at time of enrolment into the study as outlined in "New patient review" (5a) and 5.2)

Follow up data and data for ADR cases will be collected on a daily to weekly basis until discharge as outlined in "Follow up Review" and "ADR case review" (5b)

Data collection will be completed at time of discharge for all non-ADR cases. For ADR cases data collection might not be completed until after discharge from hospital, as outlined in "ADR review process".

4.5 Data handling

Data will be entered directly into the study database created for this study. The study database is stored securely on the Trust server with back up procedures described in an SOP. (to be attached)

The study team will have responsibility for: data collection, recording and quality acting under Standard Operating Procedures (SOP) in accordance with the Data Protection Act.

Data will be retained in perpetuity in light of the possibility that ADRs in children may have consequences in later life.

5 Outline of review process

Data collection will be completed by designated researchers within the study team, currently JM, KB and ST. Each week, one or two researchers will undertake new patient reviews and follow up reviews, whereas the third researcher will undertake ADR evaluations

Eligible patients will fall into one of 3 review categories:

a) New patient review (including patients discharged from PICU who were admitted to PICU from outside the hospital)

b) Follow up review (including patients discharged from PICU who were inpatient prior to PICU admission)

c) ADR suspected

a) New patient review

A new patient review involves baseline data collection and a first clinical progress review.

The purpose of the baseline data collection is to record basic demographic data required for the analysis and to create a patient profile in the study database that will enable study team members to carry out follow up reviews.

The purpose of the clinical progress review is to highlight any suspected ADRs. The focus lies on assessing any new symptoms or worsening of existing symptoms as well as assessing abnormal laboratory or imaging results in the context of all administered medication.

b) Follow up review

A follow up review involves updating the medication history and ward status and undertaking a clinical progress review to highlight any suspected ADRs.

c) ADR suspected

Any reaction highlighted as ADR suspected will be evaluated and an ADR case report will be completed.

5.1.2 Timing of new patient review and follow up review

New patients will be added to ADRIC caseload every 12 hours. New patient reviews will be carried twice daily by two members of the study team on weekdays and one member of the study team on weekends and bank holidays. New patient reviews may be postponed for 24hr or 48hrs if only one member of the study team is available and/or the workload is unusually high.

Follow up reviews will be carried out by two members of the research team on weekdays, one member of the research team on weekends and bank holidays and three members of the research team after weekends and bank holidays.

The next review date will be decided for each patient individually on a review-to-review basis. This will usually be 2 days from the time of last review.

We will aim to minimise the number reviews on weekends and bank holidays when only one member of the research team will be available for data collection. Consequently the number of reviews will be increased after Weekends and Bank Holidays when three members of the research team will be available for data collection.

5.1.3 Communicating ADRs to clinicians

Whenever a definite, probable or possible ADR is identified, the study team will report the ADR to the consultant responsible for the child's care. However, it will not be possible, practical or appropriate to inform consultants immediately about every ADR identified. Examples would include post-operative nausea and vomiting, pruritus with morphine and nausea and vomiting following chemotherapy.

These are all expected and frequent reactions we have identified during pilot work of which consultants are well aware. We will therefore only contact the consultant responsible for the child's care directly to discuss the ADR at the time the ADR is identified if

1) The ADR causality is uncertain and the case requires further discussion
2) There is a clinical reason to alert the clinician to a problem
3) We would like to recruit patient into ADRIC-QUAL (for details see ADRIC-QUAL protocol)

The consultant will receive a paper copy of the yellow card for all ADRs (5.1.4) This is expected to be the main way of communicating ADRs to clinicians who are not already aware of the ADR and where it was not necessary to contact them directly.

5.1.4 ADR reporting to the MHRA

All possible, probable or definite ADRs will be reported to the MHRA through the yellow card online reporting system on a monthly basis by one member.

5.1.5 Causality assessment

Causality assessment will be carried out using the Liverpool Causality Tool to identify the likelihood of ADR

5.1.6 Classification of suspected reactions

All suspected reactions will be coded using a standard set of MedDRA terms.

5.1.7 Review of cases deemed non-ADRs

A structured review of these cases will be undertaken to determine the number of missed ADR cases.

5% of admissions without ADRs will be assessed independently by 2 study team members.

5.1.8 Fatalities occurring within 48 hours of admission

A list of fatalities occurring within 48 hours of admission for the period of this study will be obtained from the hospital database every 4 months. The case notes of those individuals will be obtained and reviewed, in retrospect, and the database record completed as outlined in new patient review.

5.2 New patient review process: A step-by-step guide

A Meditech data file will be generated automatically for all patients newly added to ADRIC caseload (stay reaches > 48 hours). This has to be imported into the study database by the study team. The patient will then be listed in the "blank record" report.

Each new patient will fall in one of the 3 following categories and should be prioritised in the order shown:

- Patient discharged and case notes still on ward:

Complete baseline data collection, clinical progress review and enter discharge date.

If no ADR is suspected mark 'patient discharged'.

If an ADR is suspected alert ADR evaluator of the week.

- Patient still an inpatient.

Complete baseline data collection and complete clinical progress review for each completed 24hr period as outlined below.

If no ADR is suspected mark 'incomplete' and review date 'DDMMYY'. This will usually be in two days' time but researcher can elect to make it one day, three days or four days if they think this is appropriate.

- Patient discharged and case notes still not on ward.

Enter discharge date and mark 'notes needed'.

5.2.1 Baseline data

a) Personal details, admission and discharge details

Source: Meditech (These data are contained in the Meditech file for each patient which is imported into the study database at enrolment.)

Study database section: Meditech

- Hospital Unit Number
- Account number
- Name
- Date of birth
- Ward at time of import into the study base
- Age
- Gender male or female.
- Admission date
- Discharge date
- Admitting consultant
- Admitting speciality
- Admission source
- Admission time
- Duration of stay at time of import into the study database

b) Weight

Source: Meditech, patient record, observation or prescription chart

Study database section: Meditech

If the recorded weight is an estimate mark 'estimate'

If no weight has been recorded estimate weight according to Alder Hey emergency prescribing guidance [(age in years + 4) x 2] and mark 'estimate'.

Values for weight estimates will be replaced by accurate weights once these become available. The database entry cannot be closed without entering a value for weight.

c) Allergies

Source of data: Medical notes, nursing notes, prescription chart

Study database section: Allergies

Record the name of the medication the patient is allergic to.

Record type of reaction if known

If the patient is not known to have allergies mark 'NKDA' (no known drug allergies)

d) Admission type

Source: Medical notes admission

Study database section: PMH

The type of admission is determined by the reason for admission the clinical team responsible for the patient's care during admission (consultant NOT ward type).
If the patient is primarily cared for by a surgical team mark 'surgical'
If the patient is primarily cared for by a medical team mark 'medical.
If care arrangements are shared equally between both teams (for example if the patient is reviewed daily by a medical and a surgical team) mark 'both'

e) Current ward, PICU and HDU stay

Source: Meditech
Study database section: Meditech and Clinical progress section
Update name of current ward in the Meditech section if different from ward at time of enrolment. The location of the patient on any report will be linked to the current ward status.
Mark HDU or PICU for every day of stay as part of the structured clinical progress review in the following way:
Mark as 'PICU' or 'HDU' in the clinical progress section.
HDU stay does include the high dependency areas on the cardiology and neurosurgical wards and the bone marrow transplant cubicles on the oncology ward.
If the patient has been transferred from PICU or HDU to a ward with lower level of care, record the ward with the highest level of care within the given 24hr period.

f) Past Medical History and reason for admission

Source: Medical notes and nursing notes
Study database section: PMH
These data will be recorded in free text. The entry could be coded with MedDRA preferred terms in retrospect at a later stage to describe both the ADR and the non-ADR population in more detail.
Reason for admission

- For elective admissions this will be the name of the planned procedure, operation or investigation.
- For emergency admissions this will be the presenting complaint such as new presentation or exacerbation or of one or several symptoms.

Past medical history

- Any current diagnoses
- Any chronic symptoms which are still under investigation or where it has not been possible to attribute these to a diagnosis
- Previous operations
- Birth history for neonates if appropriate (gestational age at delivery, type of delivery, significant problems during delivery, details of admission to neonatal unit)

g) Medication History

Source: Prescription chart, medical notes and nursing notes
Study database section: Drug history
If the patient has not received any medication mark "no medication"
Record any topical or systemic medication administered since admission (Inclusion criteria see above) by choosing the generic name of the medication and preparation from the provided medicines list and entering the following details:

- Route of Administration
- Indication - if unclear review medical notes, nursing notes or ask member of clinical team
- Date given - for each completed 24hr period at time of review

- Dose and Number of times given per 24hr period if administered intermittently
- Dose or concentration and rate if given continuously.

If the medication administered is not in the medicines list inform JM to amend the medicines list. Complete the medication history at time of next review. The medicines list has been compiled by JM, Research Pharmacist. Every medication entry in the database will be accompanied by:

- BNF code as per current electronic BNFC version (http://bnfc.org/bnfc/)
- License status – license yes or no
- Black triangle status – black triangle yes or no
- Off label - off label prescription yes or no

For the majority of medications in the current list BNF code, licence status and black triangle status are already entered. They will auto-populate once the medication name and preparation has been entered. Any missing data as well as the off-label status will be completed by JM on a regular basis.

h) Recording of Medication administered before admission

If the patient has taken medication at home which is also prescribed during the inpatient stay mark 'on before admission'

No ADR suspected

If patient has taken medication prior to admission that is not prescribed during inpatient stay this will not be recorded

If patient has been transferred from another hospital and medication other than medication taken at home has been administered this will not be recorded

ADR suspected

If patient has taken medication prior to admission that is not prescribed during inpatient stay which is suspected to have caused and ADR which was not apparent on admission this will be recorded in the clinical progress section and/or the ADR details section.

This includes medication administered at another hospital other than medication taken at home.

5.2.2 Structured Clinical progress review

Source: as outlined below

Study database entry: clinical progress

The following sources will be reviewed

- Nursing notes
- Laboratory reports
- Imaging results
- Observation charts
- Other charts
- Prescription charts

The review will focus on the following findings

- new symptoms
- worsening of existing symptoms
- abnormal laboratory results
- abnormal imaging results
- observations outside normal limits

The aim is to compare these findings with the adverse drug reaction profile of medicines administered. The team will refer to the Summary of Product Characteristics (http://emc.medicines.org.uk/medicine/2209/SPC/Efexor/) or, if not available, the BNFC http://bnfc.org/bnfc/

If a suspicious finding could be related the adverse drug reaction profile of anaesthetic mediation and the patient has had an anaesthetic (current or previous admission) the anaesthetic charts will also be reviewed.

Naturally there are two possible outcomes for each clinical progress review:

ADR suspected or no ADR suspected.

a) ADR suspected

Enter date for each day of structured clinical review since admission or last review in the clinical progress section. Review only completed 24hr periods unless patient has been discharged.

Record symptom or abnormal result related to suspected ADR and also any treatment given or investigations undertaken. This might be several entries if more than one ADR is suspected or the suspected ADR lasted longer than 24hrs or is ongoing.

Mark the suspected medication or medications in the 'ADR? Yes' medication history section.

b) No ADR suspected

Enter the date for each day of structured clinical review since admission or last review. Review only completed 24hr periods unless patient has been discharged

5.3 Follow up review: A step-by-step guide

Patient is listed in the "review today" report and will fall into one of the 3 following categories and should be prioritised in the order shown:

- Patient discharged and case notes still on ward:

Complete medication history and ward status for all days since last review as described above

Undertake a structured clinical progress review for all days since last review as described above and enter discharge date.

If data collection has been completed the mark report status as 'patient discharged'.

- Patient still an inpatient.

Update Medication history and ward status for each completed 24 hour period since last review as described above. Undertake a structured clinical progress review for each completed 24 hour period since last review, mark 'incomplete' and set review date DD/MM/YYYY.

If ADR is suspected, mark 'ADR suspected'.

- Patient discharged and case notes not on ward.

Enter discharge date and mark 'notes needed'.

5.4 ADR case review – a step-by-step guide

This will be carried out and completed by "the ADR evaluator of the week". If a patient experiences more than one possible, probable or definite ADR during the inpatient stay each ADR might be described by a different member of the research team.

Patient will fall into one of the 5 following categories :

- Patient discharged, no results pending and case notes still on ward

Complete ADR details section and mark ADR report status as "yellow card - incomplete".

If database entry status is marked 'complete' and discharge date is entered not further action is required.

If database entry status is marked as 'incomplete', complete data as outlined above (5.2.2), enter discharge data and mark 'complete'.

- Patient discharged, results pending and case notes still on ward

Complete ADR details section as far as possible and mark ADR report status as "yellow card - incomplete"

If database entry status is marked 'complete' and discharge date is entered not further action is required.

If database entry status is marked as 'incomplete', complete data as outlined above (5.2.2er), enter discharge data and mark 'complete'.

- Patient discharged and case notes not on ward

If database entry status is marked 'complete' and discharge date is entered not further action is required

If database entry status is marked as 'incomplete' change to 'notes needed'

- Patient still an inpatient, no results pending

Complete ADR details section and mark ADR report status as "yellow card".

5.4.1 ADR details section

The ADR clinical details section or the database includes 4 sub sections:

a) Clinical details

b) ADR info

c) Causality

d) Drugs ADR

a) Clinical details section of database referring to ADR case

Reaction – Describe ADR reaction and code any findings with MedDRA preferred term(s). Past medical history details do not have to be included as these are already recorded (5.2.1f)Summarise all relevant details including

- investigations relevant to the identification and evaluation of the ADR (radiology reports, laboratory results, observations
- specific treatment for ADR
- Outcome (recovered/recovering/continuing/death/unknown)
- Duration of the ADR (unless ongoing)
- Contribution of drug or food interactions to the ADR
- Whether the ADR prolonged the admission and by how long – this is usually decided after discussion with the clinical team.
- Whether the ADR influenced the level of care (Admission to HDU cause or co-factor; Admission to PICU cause or co-factor) and if so by how long – this is usually decided after discussion with the clinical team.

Record laboratory results in the bloods section of the database

Indicate name of Investigator

Once sections a) to c) are completed change ADR status 'yellow card'

b) ADR info

This section contains questions with predefined answers such as

"Was this a serious ADR yes/no"

c) Causality

This section contains questions with predefined answers such as

Is an ADR suspected yes/no Complete Liverpool causality tool

5.5 Analysis

The will be a separate protocol for the analysis of Study 2

We will assess the number of yellow cards generated over the study period in comparison to yellow card reports for the previous 5 years (using data from MHRA) in order to provide an estimate of the degree of under-reporting.

5.6 Stopping / discontinuation rules

We do not anticipate the need for stopping or discontinuation rules. If circumstances change, the Programme Executive Group will consult the Programme Steering Committee.

6 Research Governance

Study organization:

The study lead(s) will be Prof R L Smyth, Prof M Pirmohamed, Dr M Turner, Prof A Nunn, Prof P Williamson and Dr M Peak.

The programme management group will be Prof R L Smyth, Prof M Pirmohamed, Dr M Turner, Prof A Nunn, Prof P Williamson and Dr M Peak and will meet every 6-8 weeks.

The study steering committee will comprise Sir Alasdair Breckenridge (Chair), Prof R L Smyth, Prof M Pirmohamed, Dr M Turner, Prof A Nunn, Prof P Williamson, Dr M Peak, Dr B Young, Prof D Ashby, Prof M Rieder and Dr J Raine and will meet every annually.

The study team are: Kim Bird, Jennifer Mason and Signe Thiesen and will report to the programme management group every 6-8 weeks.

7 Ethical considerations

a) Ethics approval

This is an audit project, as confirmed by NRES (letter on file). This is a review of existing data held in routine clinical records. The aim of the study is to enhance existing services using information and approaches that have been used elsewhere.

b) Consent

The information to be used is available to the investigators without permission and will be maintained, analysed and reported in a fashion from which individuals cannot be identified.

Consent will be obtained for recruitment into ADRIC-QUAL in is described in the relevant protocol.

8 Approvals

This study will be done in accord with approvals from Audit, Clinical Governance and the R&D Department at AHCH

9 Finance

Funded by National Institutes of Health Research through a Programme Grant in Applied Health Research to the Investigators and administered by the R&D Department at Alder Hey.

10 Indemnity

Standard NHS provisions

11 Reporting and dissemination

Results of this study will be:

- reported to Trust bodies (e.g. General Paediatric Forum)
- presented at regional meetings
- submitted to MHRA
- submitted for publication by peer-reviewed journals.

12. Interventions excluded after study start

a) Suspected reactions to topical anaesthetics

Excluded are reactions to lidocaine 2.5%, prilocaine 2.5% cream (EMLA®) or tetracaine 4% gel (Ametop®)

Included are reactions to LAT gel (lidocaine 4% & adrenaline 0.1% & tetracaine 0.5% gel)

Rationale: EMLA® and Ametop® are not consistently prescribed on the regular medication prescription charts. It will be difficult to obtain and record reliable data of these medications. LAT gel however is prescribed on the regular medication prescription chart.

b) Suspected reactions to Ranitidine

Excluded are reactions to Ranitidine added to TPN.

Included are reactions to Ranitidine administered otherwise.

Rationale: Ranitidine added to TPN is not consistently prescribed on the regular medication prescription charts. It will be difficult to obtain and record reliable data of these medications.

c) Suspected reactions to Heparin

Excluded are reactions to Heparin administered as intermittent intravenous heparin flush.

Included are reactions to heparin administered as intermittent intravenous injection other than heparin flush, heparin administered as continuous intravenous infusion or as subcutaneous injection.

Rationale: Heparin flushes are not consistently prescribed on the regular medication prescription charts. It will be therefore be difficult to obtain and record reliable data. In all other cases heparin is prescribed on the regular medication prescription charts.

d) Suspected reactions to rectal washouts

Excluded are reactions to rectal washouts with Sodium Chloride 0.9%.

Rationale: These are not consistently prescribed on the regular medication prescription charts. It will be therefore be difficult to obtain and record reliable data.

e) Suspected reactions to medicines administered on PICU

Excluded are suspected reactions which are apparent at time of discharge to a ward.

Included are suspected reactions to medicines administered on PICU which only become apparent after the patient's return discharge to a ward.

Rationale: ADRs occurring in an intensive care setting cannot be fully assessed using the proposed methodology and patients are therefore excluded from the study for the duration of their intensive care stay. Suspected ADRs occurring on a ward will be picked up by the study team using the proposed methodology

f) Suspected phlebitis and infusion site reactions

Excluded phlebitis and infusion site reactions

Rationale: Factors found to be strong predictors of phlebitis such as size of cannula, anatomical site and prolonged catheterisation are not recorded and we would therefore be unable to obtain reliable data. Infusion site reactions are not consistently documented in a way that would enable the study team to distinguish a reaction due to error or extravasation from a true infusion site reaction.