Methods

Key findings

- The 6th National Audit Project of the Royal College of Anaesthetists examined the incidence, predisposing factors, management, and impact of life-threatening perioperative anaphylaxis.
- NAP6 included: a national survey of anaesthetists’ experiences and perceptions, a national survey of allergy clinics, a registry collecting detailed reports of all Grade 3–5 perioperative anaphylaxis cases for one year, and a national survey of anaesthetic workload and perioperative allergen exposure.
- NHS and independent sector hospitals were approached to participate.
- Cases were reviewed by a multidisciplinary expert panel (anaesthetists, intensivists, allergists, clinical immunologists, patient representatives and stakeholders) using a structured process designed to minimise bias.
- Clinical management and investigation were compared with published guidelines.
- This chapter describes detailed study methods and reports on project engagement by NHS and independent sector hospitals.
- The methodology includes a new classification of perioperative anaphylaxis, and a new structured method for classifying suspected anaphylactic events and the degree of certainty with which a causal trigger agent can be attributed.
- NHS engagement was complete (100% of hospitals).
- Independent sector engagement was limited (13% of approached hospitals).
- We received more than 500 reports of Grade 3–5 perioperative anaphylaxis, with 266 suitable for analysis.

A number of factors mean that data from historical studies or from other geographical locations may not be transferable to current practice or UK practice. No major prospective study of perioperative anaphylaxis has previously been performed in the UK.

The National Audit Projects of the Royal College of Anaesthetists have an established role in examining clinically important, rare complications of anaesthesia that are incompletely studied [Cook 2009, 2011a, 2011b, 2014; Pandit 2014a, 2011b]. The established methodology of the National Audit Projects (NAPs) is to perform a national survey or surveys of relevant national activity [Sury 2014; Kemp 2017] and establish a national registry for reporting of relevant cases for a time-limited period. This enables an examination of (a) pre-existing practices and beliefs, (b) relevant activity (denominator data), and (c) a large cohort of relevant cases (numerator data); and thence (d) incidence data.

Methods

The 6th National Audit Project (NAP6) was commissioned by the Health Services Research Centre (HSRC) of the National Institute of Academic Anaesthesia for the Royal College of Anaesthetists (RCoA). It is the sixth in a series of national audits (though these are more correctly described as service evaluations) conducted by the specialty.

The topic for NAP6 was selected by open tender for proposals in 2013. There were 91 proposals covering 33 topics [Cook 2013]. The topic of perioperative anaphylaxis was selected by a committee composed of members of the HSRC executive board.

The intention of the project was to establish:

- What proportion of cases of suspected perioperative anaphylaxis are referred and or investigated?
- What proportion of investigated cases is proven or unproven?
- How well does management, referral and investigation match published guidelines?
- Is there any correlation between drugs used in resuscitation, (e.g. adrenaline, alpha-agonists, vasopressin) and outcome for severe cases?

The methodology of NAP6 is similar to, and builds upon, that used for NAP3, NAP4, and NAP5 [Cook 2009, Cook 2011a, Pandit 2014a].

The NAP6 project was approved by Confidentiality Advisory Committee of the NHS Health Research Authority, the National and Local Caldicott Scrutiny Processes in Scotland, and the Privacy Advisory Committee for Northern Ireland. The Confidential Advisory Committee deals with approvals for the handling of patient-identifiable information across the NHS. If such information...
As we only wished to collect cases of life-threatening anaphylaxis, it was emphasised that only anaphylaxis Grades 3–5 (Table 1) were to be included. Cases were to be included irrespective of age or hospital location, but patients in critical care or the emergency department were excluded unless undergoing procedural general anaesthesia.

Table 1. Grading of perioperative hypersensitivity/anaphylaxis used for determining inclusion or exclusion in the NAP6 project

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
<th>NAP6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not life-threatening</td>
<td>Rash, erythema and/or swelling</td>
</tr>
<tr>
<td>2</td>
<td>Not life-threatening</td>
<td>Unexpected hypotension — not severe, eg, not requiring treatment and/or bronchospasm — not severe, eg, not requiring treatment +/- Grade 1 features</td>
</tr>
<tr>
<td>3</td>
<td>Life-threatening</td>
<td>Unexpected severe hypotension and/or severe bronchospasm and/or swelling with actual or potential airway compromise +/- Grade 1 features</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening</td>
<td>Fulfilling indications for CPR</td>
</tr>
<tr>
<td>5</td>
<td>Fatal</td>
<td>Fatal</td>
</tr>
</tbody>
</table>

Each month the LC was required to provide the central NAP6 team with a monthly ‘return’ indicating the number of reports of suspected life-threatening perioperative anaphylaxis identified that month, using a system developed by the UK obstetric surveillance system (Knight 2007) and also used in NAPS (Pandit 2014a). Where no reports were received the LCs returned a ‘nil’ report.

Presentations, posters and promotional material were provided to each LC, and the project was widely advertised nationally (Figure 1). Information provided to LCs included advice on interpretation of grades of anaphylaxis and a series of ‘frequently asked questions’, with answers. For example, LCs were advised to regard hypotension that was mild or required modest doses of a vasopressor or fluid as meeting the definition of Grade 2, whereas hypotension that was profound, sustained, resistant to treatment, or requiring extensive treatment met the criteria for Grade 3.

### Methods

is required, then approvals are required under Section 251 of its governance procedures. Since no patient-identifiable information was used, no Section 251 application was necessary. The National Research Ethics Service confirmed it to be a service evaluation, not requiring formal ethical approval. The project received the endorsement of all four Chief Medical Officers of the UK.

All hospitals in the UK performing surgical procedures with anaesthetist involvement were contacted. This included 356 UK NHS hospital centres and 304 independent sector hospitals believed to perform surgical work. All NHS centres volunteered a Local Coordinator (LC) – a consultant anaesthetist who became responsible for delivering the project at their hospital and for liaising with the central NAP6 team. Several LCs were responsible for more than one hospital within a Trust (England, Northern Ireland) or Board (Scotland, Wales). During efforts to engage with the independent sector hospitals more than 300 hospitals were contacted on several occasions.

There were four elements to the project. First, a baseline survey collected retrospective data on anaesthetists’ previous experiences with perioperative anaphylaxis, and their perceptions and patterns of risk avoidance (Kemp 2017 and Chapter 7). Second, UK allergy clinic services were surveyed to identify clinics that investigated suspected perioperative anaphylaxis and to compare their practices against guidelines (Egner 2017 and Chapter 13). Third, the main prospective study collected anonymised case reports of risk avoidance (Kemp 2017 and Chapter 7). Second, UK allergy clinic services were surveyed to identify clinics that investigated suspected perioperative anaphylaxis and to compare their practices against guidelines (Egner 2017 and Chapter 13). Third, the main prospective study collected anonymised case reports over a one-year period. Fourth, a prospective survey, also in 2016, of all NHS centres volunteered a Local Coordinator (LC) – a consultant anaesthetist who became responsible for delivering the project at their hospital and for liaising with the central NAP6 team. Several LCs were responsible for more than one hospital within a Trust (England, Northern Ireland) or Board (Scotland, Wales). During efforts to engage with the independent sector hospitals more than 300 hospitals were contacted on several occasions.

LCs were sent detailed information (available at http://www.nationalauditprojects.org.uk/NAP6-Resources#pt) and were tasked with disseminating and coordinating all phases of the project locally.

All allergy clinics investigating perioperative anaphylaxis were contacted and informed of the project. Materials were made available to enable them to give LCs detailed information about tests performed and their results when investigating suspected perioperative anaphylaxis.

LCs were asked to ensure the reporting of all cases of suspected life-threatening perioperative anaphylaxis to the NAP6 team. Anaphylaxis was defined as ‘a severe, life-threatening, generalised or systemic hypersensitivity reaction’. Perioperative anaphylaxis was defined as:

Anaphylaxis which occurs in patients undergoing a procedure requiring general or regional anaesthesia or sedation or managed anaesthesia care (anaesthetist monitoring only) under the care of an anaesthetist between the period of first administration of a drug (including premedication) and the post-procedure transfer to the ward, or critical care.
Reporting cases

Reporting was in two parts.

Part A included details of the patient, drugs administered, the clinical features, management and timings relating to the event, outcomes, contributory factors, referral for investigation, and details of reporting of the event and communication to the patient. LCs were asked to submit Part A as soon as possible after the suspected anaphylactic event. Definitions of clinical features associated with anaphylaxis that should be reported were provided in the webpage supporting information (Table 2).

Table 2. Definitions of clinical features

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>Absence of effective cardiac output</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Fall in blood pressure greater than could be explained by coexisting co-morbidities, neuraxial blockade, or daily medication</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Wheeze and/or raised ventilatory pressure greater than could be readily explained by coexisting co-morbidities</td>
</tr>
<tr>
<td>Cyanosis/ oxygen desaturation</td>
<td>Subjective appearance of cyanosis or unexpected fall in SpO₂</td>
</tr>
<tr>
<td>Reduced/absent capnography trace</td>
<td>Unexpected low amplitude of capnography trace, or absent trace</td>
</tr>
<tr>
<td>Flushing/non-urticarial rash</td>
<td>Erythema or non-raised rash</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Raised wheals</td>
</tr>
<tr>
<td>Laryngeal oedema</td>
<td>Glottic swelling seen at laryngoscopy or stridor suggestive of glottic swelling</td>
</tr>
<tr>
<td>Swelling/oedema (non-laryngeal)</td>
<td>Any other swelling</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Rise in heart rate not readily explicable by coexisting co-morbidities or a light plane of anaesthesia</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Fall in heart rate not readily explicable by coexisting co-morbidities, concomitant drug administration, coexisting beta adrenergic blockade, or vagal reflex</td>
</tr>
<tr>
<td>Patient feeling unwell</td>
<td>The awake patient complains of acutely feeling unwell</td>
</tr>
<tr>
<td>Itching</td>
<td>The awake patient complains of itching</td>
</tr>
</tbody>
</table>
Methods

**Review of cases**

The NAP6 panel met monthly to review and classify cases. The panel was composed of 25 representatives of patient support groups, patient representatives, and clinicians in relevant fields (anesthesia, critical care, allergy, immunology) representing stakeholder and subspeciality organisations. Clinicians were selected by stakeholder organisations and, while many had specific expertise in allergy, this was not a requirement for joining the panel.

The panel reviewed each case in detail and in a structured manner, three times. First, the clinical care (Part A) was reviewed by a small group of 3–5 clinical and patient representative panel members. Second, Allergists and Immunologists reviewed drug administration and allergy investigations (relevant parts of Part A and all of Part B). Several groups performed these tasks on different cases concurrently. The outputs of the reviews were used to populate a structured output form (Appendix 1) and spreadsheet for subsequent analysis. When sufficient cases were reviewed, all groups joined into a large panel – typically 12-15 panel members – and the cases were again reviewed to combine the outputs of the clinical and allergy/immunology reviews, and to check and moderate each small group’s findings.

This process was used in an attempt to avoid ‘outcome bias’ (where the known poor outcome leads to an unreasonably harsh judgement) [Caplan 1991], ‘hindsight bias’ (where retrospective review leads to a tendency to believe that an adverse outcome was predictable or avoidable) [Henriksen 2003] and ‘groupthink’ (where a desire to agree within groups leads to a lack of independent scrutiny) [Turner 1998].

In judging quality of care, we referred to guidelines from:

- The Association of Anaesthetists of Great Britain and Ireland on management of suspected anaphylaxis associated with anaesthesia [Harper 2009]
- The Resuscitation Council (UK) on management of anaphylaxis [RCUK 2016]
- The European Resuscitation Council on cardiopulmonary resuscitation [Soar 2015]
- The British Society for Allergy and Clinical Immunology (BSACI) guidelines on investigation of anaphylaxis during general anaesthesia [Ewan 2010].

In addition, the review panel referred, where appropriate to NICE Clinical Guidance – NICE CG183 Drug allergy: diagnosis and management of drug allergy in adults, children and young people [NICE 2014, Dworzynski 2014], and NICE CG134 Anaphylaxis: assessment and referral after emergency treatment [NICE 2011].

As these guidelines were used to measure deviation from standards of care, NAP6 had a greater genuine ‘audit’ component than previous NAPs. Overall quality of care (initial management, clinic referral by anaesthetist and allergy clinic investigation) were also each judged as ‘good’, ‘poor’, ‘good and poor’ or ‘unassessable’ based on adherence to guidelines, and ultimately by panel consensus.

It became rapidly apparent that cardiopulmonary resuscitation (CPR) was frequently not started when there was profound hypotension. We therefore defined a systolic blood pressure, below which we judged that CPR should be started, which we set at 50 mmHg (see discussion). These cases were classified as Grade 4. When CPR was not started, we judged this as failure to initiate CPR when indicated, and judged this to be a deviation from resuscitation guidelines.

The case report form included specific questions about potential errors related to allergy history or administration of cross-reacting substances. Preventability of each case was classified as ‘yes’, ‘no’, or ‘uncertain’, and reasons for the judgement that the event could have been prevented were recorded.

Patient outcomes were measured in two ways. Individual patient outcomes were captured on the case report form, including new anxiety about future anaesthetics, symptoms consistent with post-traumatic stress disorder, change in mood, impaired memory, impaired coordination, impaired mobility, myocardial infarction, heart failure, renal impairment, and stroke. Overall severity of patient outcome, was recorded using the National Patient Safety Agency (NPSA) classification of severity of harm from patient incidents shown in Table 3 (NPSA 2008). In most cases Grade 3 anaphylaxis itself meets the definition of moderate harm. When resuscitation had only involved minimal doses of vasopressor or other drugs and no further action had been taken, the case was deemed to meet the criteria for minimal harm. Apparently permanent sequelae (ie. persisting symptoms or deficits at follow-up) were recorded as severe harm, as were cardiac arrest and ICU stay of more than 14 days.

**Table 3. Degree of physical harm**

Modified from: NPSA Seven steps to patient safety [NPSA 2008].

<table>
<thead>
<tr>
<th>Severity grade</th>
<th>Description (tick against the most severe feature)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertain</td>
<td>Insufficient information</td>
</tr>
<tr>
<td>Mild</td>
<td>Minimal harm necessitating extra observation or minor treatment*</td>
</tr>
<tr>
<td>Moderate</td>
<td>Significant, but not permanent harm, or moderate increase in treatment** Includes delayed cancer surgery</td>
</tr>
<tr>
<td>Severe</td>
<td>Permanent harm due to the incident***, including cardiac arrest; adverse sequelae recorded as ‘Severe’ in Part A or Part B; ICU stay of 14 days or longer</td>
</tr>
<tr>
<td>Death</td>
<td>Death due to the incident</td>
</tr>
</tbody>
</table>

* first aid, additional therapy, or additional medication. Excludes extra stay in hospital, return to surgery, or re-admission.
** return to surgery, unplanned re-admission, prolonged episode of care as inpatient or outpatient, or transfer to another area such as Intensive Care.
*** permanent lessening of bodily functions, sensory, motor, physiologic or intellectual.
Table 4. Immunological classification of reports to NAP6

<table>
<thead>
<tr>
<th>Class of event</th>
<th>High certainty</th>
<th>Intermediate certainty</th>
</tr>
</thead>
</table>
| **Allergic anaphylaxis** *(IgE-mediated)* | Timeline – within 60 min  
Evidence of mast cell mediator release tryptase  
Evidence of positive sIgE (blood or skin tests)*  
4/4 criteria; *essential | Timeline – within 60 min  
Evidence of mast cell mediator release tryptase  
Evidence of positive sIgE (blood or skin tests)*  
Differential diagnoses excluded  
3/4 criteria; *essential |
| **Non-allergic anaphylaxis** *(non-IgE-mediated)* | Timeline – within 60 min  
Evidence of mast cell mediator re-release tryptase (see note 2)  
No evidence of positive sIgE (blood or skin tests)  
Differential diagnoses excluded  
4/4 criteria | Timeline – within 60 min  
Evidence of mast cell mediator re-release tryptase  
No evidence of positive sIgE (blood or skin tests)  
Differential diagnoses excluded  
3/4 criteria |
| **Anaphylaxis - mechanism uncertain** | Meeting 2/3 criteria in 3 above, and/or  
Differential diagnoses more likely:  
Airway management  
Drug side effect  
Drug overdose  
Cardiac disease/event  
3/3 criteria | - |
| **Anaphylaxis uncertain** | Meeting 2/3 criteria in 3 above, and/or  
Differential diagnoses more likely:  
Airway management  
Drug side effect  
Drug overdose  
Cardiac disease/event  
3/3 criteria | - |
| **Not anaphylaxis** | Not meeting clinical criteria for diagnosis [as per grading] | - |

Each event was classified as ‘allergic anaphylaxis’, ‘non-allergic anaphylaxis’, ‘anaphylaxis mechanism uncertain’, ‘anaphylaxis uncertain’ or ‘not anaphylaxis’ using the classification shown in Table 4.

In order to classify the type of each event, a definition of ‘mediator release’ was required. Providing mast cell tryptase samples were taken at appropriate times after the event [broadly: soon after the event and approximately 1 to 3 hours after the event and a baseline sample either taken before the event or ≥24 hours after the event] the following definition was used:

- Peak mast cell tryptase ≥1.2 x nadir value + 2µg.L⁻¹ (Valent 2012) or
- Peak mast cell tryptase ≥14 µg.L⁻¹ [ie, >99th centile for normal mast cell tryptase levels] (Egner 2016).

This was a pragmatic definition, and made in the knowledge that the second part of the definition might not fully exclude a very small number of cases of mastocytosis.

Where there was uncertainty, differential diagnoses other than anaphylaxis were carefully considered by the full review panel.

In determining adequacy of allergy clinic investigation, BSACI guidelines (NICE 2014, Mirakian 2009 and 2015) were used by the immunologists and allergists to set the following rules.

- Where testing for allergy to a neuromuscular blocking agent (NMBA) was necessary, given variable access to some NMBA’s the NAP6 ‘minimum panel of NMBA’s’ (Egner 2017) was applied: suxamethonium, rocuronium and either atracurium or cisatracurium should have been tested, and at least one safe alternative should have been sought.
- Chlorhexidine and latex should have been investigated routinely because of the widespread risk of exposure.
- For skin prick tests (SPTs) and intradermal tests (IDTs) to be judged appropriate, there should be no tests performed that were not indicated. This was to exclude ‘scatter-gun’ testing being judged as good practice.
- Allergy to antibiotics and particularly beta-lactams could only be excluded if a negative skin test was followed by negative provocation testing.
The allergists and immunologists reviewed each case that was confirmed to be anaphylaxis, to determine all possible causative agents (culprits). Reviewing the clinical data and allergy clinical tests, they identified these drugs as having high, intermediate or low culpability.

We recorded 'identified culprits' as follows:

- **Definite**: where one sole agent was recorded with a high degree of confidence and any other agents with intermediate or low confidence.
- **Probable**: where:
  - Only one agent was recorded with an intermediate degree of confidence and any other agent was identified with low confidence
  - Two agents were both recorded with a high degree of confidence
- **Possible**: where two agents were recorded with an intermediate degree of confidence and none with a high degree of confidence.
- **Do not count**: where:
  - More than two agents were recorded with a high degree of confidence
  - More than two agents were recorded with an intermediate degree of confidence
  - The only agents recorded were identified with a low degree of confidence.

Agents meeting the criteria for Definite or Probable were considered to be 'identified culprits': agents meeting the criteria for Possible or Do not count, were not.

Approximately 10–12 cases were fully reviewed each day in the early part of the review process, increasing to up to 22 per day in the latter stages as the panel became more familiar with the process. Due to the high number of cases submitted we were not able to perform full reviews of all cases. The remaining cases in the main dataset had a briefer review that determined: the diagnosis of anaphylaxis, the grade of anaphylaxis, all potential culprits, and 'identified culprits'.

### Results

The results of the Allergy clinic baseline survey (Egner 2017, Chapter 13), Anaesthesia baseline survey (Kemp 2017, Chapter 7) Anaesthetic Activity Survey (Chapter 8) and Allergen Survey (Chapter 9) are each reported separately and are not considered further here.

There were no technical or security breaches of the website, or concerns about identification of patients, clinicians or hospitals.

All 356 (100%) NHS hospitals where surgery was undertaken agreed to take part in the project and volunteered an LC. These 356 hospitals were served by 282 LCs. Eighty-four percent of NHS hospitals returned all scheduled monthly reports: the overall return rate of scheduled monthly reports from these independent sector hospitals was 70%.

In view of the small number of independent sector hospitals that agreed to participate, it was decided that this sample would not be representative of practices or events in this healthcare sector and a decision was made to include their data only for examination of isolated events and not for numerical analysis.

The full results of analysis and the findings of reports of anaphylaxis are presented in the accompanying chapters. We present here the results of the NAP6 process.

There were 628 requests made for login details to the reporting website. A total of 541 cases were submitted: 412 with Part A and Part B completed or fatalities, 125 survivors with only Part A completed, and four with only Part B completed. Amongst these there were seven requests for an identifier for the reporting website from independent sector hospitals but only two cases were fully reported. These cases were not included in the main dataset.

Only those cases with Part A and Part B (n=402), or deaths (n=10) were considered for review. Of these, 93 were not suitable for review due to lack of detail or not meeting entry criteria, 27 were uninterpretable, 15 were not anaphylaxis, nine were excluded as being Grade 2, and two were from independent sector hospitals.

A total of 266 [256 with Part A and B and 10 fatalities] NHS cases met inclusion criteria, were interpretable, and were Grade 3–5 anaphylaxis: these formed the main dataset.

A total of 217 cases were fully reviewed, including 184 of the main dataset. The remaining 82 cases underwent limited review, as described above.

### Figure 2. Flowchart of included cases

Log in detail requested = 628

Cases reported = 541

Cases with Part A & B (402) and fatal cases (10) = 412

Included in final dataset = 266

Survivors with no Part B = 125

No Part A = 4

Lack of detail / not meeting criteria = 93

Uninterpretable = 27

Not anaphylaxis = 15

Grade 2 = 9

Independent sector = 2
Discussion

NAP6 is likely to be the most comprehensive prospective study of perioperative anaphylaxis ever undertaken. It provides prospective data on a large number of cases which have all been subject to structured multidisciplinary expert review. It presents the opportunity to learn about preparedness of hospitals and clinicians, clinical presentation of perioperative anaphylaxis, severity, immediate management, referral for investigation, and outcomes. It collates significant epidemiological data about distribution of anaphylaxis grade, suspected and actual triggers, and non-standard treatments. Further, it describes the quality of management and investigation in a 'real world' setting, and of communication between clinicians and with patients.

In order to collect and analyse these data in a meaningful manner it was important to perform a structured analysis of cases. That structure was underpinned by clear definitions of which events should be included or excluded, and also by classification during review. We followed the review process previously used in previous NAPs which included multiple, serial, multidisciplinary reviews incorporating patient representation, formal moderation and a structured output. Review of events that have already happened is always prone to the limitations of 'looking backwards' and this may be exacerbated when the outcome of the event is known. Our processes made every effort to produce balanced judgements, accepting these known limitations.

Anaphylaxis is "a severe, life-threatening generalised hypersensitivity reaction" (Johansson 2003). Lesser hypersensitivity reactions should not be included in the term anaphylaxis. Unlike many previous large-scale studies of hypersensitivity we have focused only on genuinely life-threatening reactions [ie. true anaphylaxis]. We judged this would enable us to gather the most clinically powerful lessons, to improve engagement in the project and to increase capture rates. These are also the cases where most is to be gained (or lost) in efforts to improve care.

There are numerous gradings scales and definitions of severity of hypersensitivity/anaphylaxis and the cut-offs between grades vary considerably. This has implications for data analysis and comparisons between studies. Ring and Messmer’s 1977 classification included four grades, with Grade 3 defined as "shock, life-threatening spasm of smooth muscles [bronchi, uterus etc.]", and Grade 4 as "cardiac and/or respiratory arrest" (Ring 1977). Garvey in 2001 described only three grades with the highest grade [Grade 3], including all "Very severe reactions requiring prolonged treatment, eg, anaphylactic shock, usually, but not always, involving two or more organ systems" (Garvey 2001). Mertes in 2003 included in Grade 3 the life-threatening events – "cardiovascular collapse, tachycardia or brady cardia, arrhythmias, severe bronchospasm", and in Grade 4 "circulatory inefficacy, cardiac and/or respiratory" (Mertes 2003). In 2007 Krøigaard introduced Grade 5: fatal anaphylaxis (Krøigaard 2007). A consensus on diagnostic criteria for definition of anaphylaxis was reported in 2006 but this has significant limitations if applied to perioperative anaphylaxis (Sampson 2006). In 2010 yet another classification was published – classifying all hypotension as Grade 4 (Cox 2010).

Despite this apparent surfet of grading systems, we found none that was entirely clear or satisfactory, and developed the classification shown in Table 1. This classification aimed specifically to accommodate the normal variations in vital signs and physiology that can be seen in the perioperative setting, particularly in elderly, frail or co-morbid patients. The NAP6 classification of perioperative hypersensitivity and anaphylaxis uses the pragmatic terms ‘unexpected’ and ‘severe’ in the belief that anaesthetists can distinguish the usual from the unusual, and a reaction requiring rescue treatment from one which does not. We used a clear cut-off for Grade 4, ie. if indications for initiating CPR are fulfilled. During the NAP6 project another group published a new classification, and this also usefully reviews many of the existing classifications and their limitations in respect to perioperative anaphylaxis (Rose 2016). This used three Grades A–C: Grade A is not life threatening and therefore does not meet the accepted definition of anaphylaxis, and Grade B includes some Grade 2–3 characteristics of other groups, with Grade C being similar to Krøigaard’s Grade 4.

During early case reviews it became apparent that ‘indication for CPR’ might not be as clear-cut as we had thought. The case report form asked both for the lowest blood pressure recorded and whether CPR was started. In a large number of cases the lowest systolic blood pressure was very low, often being <60 mmHg or <50 mmHg or even unrecordable, but CPR was not performed. This was discussed at length in the panel. We took external advice from experts in resuscitation and anaphylaxis, and their guidelines and concluded that it was logical to set a lowest systolic blood pressure at which it was reasonable to set a lowest systolic blood pressure at which it was reasonable to set CPR should start in adult patients. In the awake patient it is now routine to start CPR when ‘there are no signs of life/signs of responsiveness’. As perioperative anaphylaxis most commonly takes place after induction of anaesthesia, these signs are absent. In invasively monitored patients a blood pressure of <50 mmHg is predictive of central and peripheral pulselessness (Deakin 2000), which should trigger CPR. As non-invasive blood pressure monitors tend to over-estimate the blood pressure in severe hypotension, a non-invasive blood pressure recording of ≤50 mmHg implies that the true blood pressure is even lower. We therefore judged that when the lowest systolic blood pressure was <50 mmHg, CPR was indicated. This rule was then applied to all adult cases. These cases were recorded as Grade 4, and if CPR was not started recorded as ‘CPR not started when indicated’. The case report form asked both for the lowest blood pressure recorded and whether CPR was started. In a large number of cases the lowest systolic blood pressure was very low, often being <60 mmHg or <50 mmHg or even unrecordable, but CPR was not performed. This was discussed at length in the panel. We took external advice from experts in resuscitation and anaphylaxis, and their guidelines and concluded that it was logical to set a lowest systolic blood pressure at which it was reasonable to set CPR should start in adult patients. In the awake patient it is now routine to start CPR when ‘there are no signs of life/signs of responsiveness’. As perioperative anaphylaxis most commonly takes place after induction of anaesthesia, these signs are absent. In invasively monitored patients a blood pressure of <50 mmHg is predictive of central and peripheral pulselessness (Deakin 2000), which should trigger CPR. As non-invasive blood pressure monitors tend to over-estimate the blood pressure in severe hypotension, a non-invasive blood pressure recording of ≤50 mmHg implies that the true blood pressure is even lower. We therefore judged that when the lowest systolic blood pressure was <50 mmHg, CPR was indicated. This rule was then applied to all adult cases. These cases were recorded as Grade 4, and if CPR was not started recorded as ‘CPR not started when indicated’. We also judged this to be a deviation from (resuscitation) guidelines and recorded whether this was the only such deviation. This group of patients (lowest systolic blood pressure and no CPR) were examined as a separate cohort to explore whether their outcomes differed from other patient groups (Chapter 12, Deaths, cardiac arrest, and profound hypotension). The NAP6 classification of grade of anaphylaxis was therefore updated to include this critical blood pressure cut-off (Table 5).
Table 5. Grading of perioperative hypersensitivity/anaphylaxis used for analysis in the NAP6 project

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
<th>NAP6</th>
</tr>
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<tbody>
<tr>
<td>1 Not life-threatening</td>
<td>Rash, erythema and/or swelling</td>
<td>Excluded</td>
</tr>
<tr>
<td>2 Not life-threatening</td>
<td>Unexpected hypotension – not severe, e.g., not requiring treatment and/or bronchospasm – not severe, e.g., not requiring treatment +/- Grade 1 features</td>
<td>Excluded</td>
</tr>
<tr>
<td>3 Life-threatening</td>
<td>Unexpected severe hypotension and/or severe bronchospasm and/or swelling with actual or potential airway compromise +/- Grade 1 features</td>
<td>Included if perioperative anaphylaxis suspected</td>
</tr>
<tr>
<td>4 Life-threatening</td>
<td>Fulfilling indications for CPR including systolic blood pressure &lt;50 mmHg</td>
<td>Included if perioperative anaphylaxis suspected</td>
</tr>
<tr>
<td>5 Fatal</td>
<td>Fatal</td>
<td>Included if perioperative anaphylaxis suspected</td>
</tr>
</tbody>
</table>

In the analysis of investigation of anaphylaxis, the allergists and immunologists on the panel required a clear way to classify the type of immunological event, and devised that shown in Table 4. The presence of a dynamic tryptase rise was determined using an accepted consensus method (Valent 2012), which has (since NAP6 started) been confirmed to have high specificity (78%), positive predictive value (98%), and a moderate negative predictive value (44%) in perioperative anaphylaxis (Baretto 2017). Where there was no dynamic rise in tryptase, we used a value of >99th centile as indicating elevation; this has been shown to improve sensitivity of the above test (Egner 2016). This goes well beyond previous reports which have often simply classified cases as ‘IgE-mediated’ (hypersensitivity with skin prick test positive), ‘non-IgE-mediated’ (hypersensitivity with skin prick test negative), or ‘unclassified’. Assessing the utility and quality of the allergy clinic investigation was further aided by including the consensus view that the NAP6 minimum panel of NMBAs (Egner 2017) should be used, and that allergy to both chlorhexidine and latex should be tested routinely because of their widespread (and often hidden) presence in healthcare settings (Egner 2017, Ewan 2010, Scolaro 2017, Mertes 2011). Finally, we used a structured method to define the degree of certainty with which culprit agents were identified, and only included those that were Definite or Probable culprits in reporting our findings.

The published guidelines selected for providing standards against which the quality of practice was assessed (Harper 2009, RCUK 2016, Soar 2015, NICE 2011, NICE 2014) were chosen to encompass immediate resuscitation (including from cardiac arrest), secondary clinical management, referral to an allergy clinic, primary and specialist allergy investigation, record keeping, and communication with patients and healthcare professionals. UK guidelines were selected, being the most relevant to the patient population being studied.

Using this method, we received more than 500 reports of perioperative anaphylaxis. We were able to include 266 cases and identify 199 culprit agents in 192 cases. Our findings are discussed in context and with full numerical analysis in the following chapters.

As with previous NAPs, NAP6 is the product of a concerted national effort by all departments of anaesthesia in the UK, and, through its various phases, the vast majority of UK anaesthetists. This project has also involved considerable multidisciplinary working with both allergists and immunologists. The project could not take place without the generous voluntary efforts of many people and we acknowledge that here and offer them our thanks. The NAPs require anaesthetists to report cases where a significant critical incident has occurred, and harm may have come to the patient.

We rely on anaesthetists’ openness and honesty. The NAP6 panel, including the clinical lead, had no access to any identifiable information regarding the geographical source of any report, the identity of the reporter, or any patient, hospital or clinician identifiable details. This anonymity, embedded within the project design, remains central to its success.
References


### Appendix 1:
### Panel review form

**Date of review:**

Does the report meet the inclusion criteria?  
If no, why?  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

Might it be a duplicate?  
If yes, action taken:  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

Is the report interpretable?  
If no, action taken:  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

Timing of event (“induction” refers to first drug/substance administered by the anaesthetist):

- [ ] Pre-induction  
- [ ] After induction and before surgery/intervention  
- [ ] During surgery/intervention  
- [ ] After completion of surgery/intervention

Class of event (as determined by review panel):

- [ ] Allergic anaphylaxis  
- [ ] Non-allergic anaphylaxis  
- [ ] Anaphylaxis, mechanism uncertain  
- [ ] Not anaphylaxis  
- [ ] Uncertain  
- [ ] Not stated

Class of event (as determined by allergy clinic):

- [ ] Allergic anaphylaxis  
- [ ] Non-allergic anaphylaxis  
- [ ] Anaphylaxis, mechanism uncertain  
- [ ] Not anaphylaxis  
- [ ] Uncertain  
- [ ] Not stated

Grade of event as determined by review panel:  

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Uncertain</th>
</tr>
</thead>
</table>

**Immediate care (tick)**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>N/A</th>
</tr>
</thead>
</table>
| Resuscitation by anaesthetist of appropriate grade  
Prompt recognition of critical event  
Prompt recognition of anaphylaxis  
Appropriate airway management  
Prompt pharmacological treatment for anaphylaxis  
Comprehensive pharmacological treatment for anaphylaxis  
Prompt initiation of cardiac compressions  
Administration of adrenaline when indicated  
Appropriate iv fluid management  
Suspected culprit agent discontinued promptly  
Actual culprit agent discontinued promptly  
Intervention abandoned appropriately |
Clinical management by the anaesthetist:

- Good
- Poor
- Good and poor
- Unassessable

### Subsequent care (tick)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer to different hospital for HDU/ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written information given to patient prior to clinic appointment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate MCT samples requested</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate MCT results available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigation impacted by unactioned MCT sample request(s)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the patient referred to an allergy clinic if appropriate?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was adequate information provided to the allergy clinic at referral?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the clinic waiting time significantly detrimental to the patient?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient given information by anaesthetist prior to clinic appointment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient given hazard warning, eg, Medic Alert by anaesthetist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case reported to MHRA by anaesthetist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Referral to allergy clinic:

- Good
- Poor
- Good and poor
- Unassessable

### Allergy clinic investigation (tick)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>N/A Unclear</th>
<th>If no specify</th>
</tr>
</thead>
<tbody>
<tr>
<td>All potential culprits investigated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufficient panel of muscle relaxants*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorhexidine investigated*</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latex investigated*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate SPTs*</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate IDTs*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Appropriate blood tests</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Was it necessary to measure baseline MCT in clinic</td>
<td></td>
<td></td>
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<tr>
<td>Appropriate challenge tests</td>
<td></td>
<td></td>
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<tr>
<td>Appropriate advice on future avoidance</td>
<td></td>
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<tr>
<td>Written information to patient, eg, copy of clinic letter</td>
<td></td>
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<tr>
<td>Clinic letter to anaesthetist</td>
<td></td>
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<tr>
<td>Clinic letter to GP</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patient given Hazard Warning, eg, Medic Alert by clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case reported to MHRA by clinic</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*see crib sheet

### Referral to allergy clinic:

- Good
- Poor
- Good and poor
- Unassessable

### Culprit agent(s)

<table>
<thead>
<tr>
<th>Identity of drugs/substance suspected by:</th>
<th>Drug/substance 1</th>
<th>Certainty \ H/I/L/Not stated</th>
<th>Drug/substance 2</th>
<th>Certainty \ H/I/L/Not stated</th>
<th>Unable to identify (tick)</th>
<th>Not recorded (tick)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthetist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy clinic</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review panel</td>
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<td></td>
<td></td>
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</tbody>
</table>
Methods

CONTRIBUTORY AND CASUAL FACTORS

Specific (tick those that apply)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete pre-intervention allergy history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-intervention allergy history not heeded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibility of cross-sensitivity not heeded</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>A previous reaction was not appropriately investigated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Was the index event preventable?  ☐ Yes  ☐ No  ☐ Uncertain
If yes, how might it have been prevented?

If there was a further reaction, could it have been prevented?  ☐ Yes  ☐ No  ☐ Uncertain  ☐ N/A
If yes, how might it have been prevented?

SEVERITY OF PHYSICAL HARM (NPSA)

This is the harm occasioned by the whole episode (see crib sheet)

<table>
<thead>
<tr>
<th>Severity grade</th>
<th>Description (tick against the most severe feature)</th>
<th>Tick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertain</td>
<td>Insufficient information</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>No harm (whether lack of harm was due to prevention or not)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Minimal harm necessitating extra observation or minor treatment</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Significant, but not permanent harm, or moderate increase in treatment</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Permanent harm due to the incident</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>Death due to incident</td>
<td></td>
</tr>
</tbody>
</table>

Lessons to be learned:

Any possible recommendations arising:

Amend Summary Narrative  ☐ Yes  ☐ No

Action taken:

Consider: Any further information needed. If yes, action taken:

Is this case suitable for a vignette?  ☐ Yes  ☐ No
If yes, why?

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