Public Assessment Report of the Commission on Human Medicines' Adrenaline Auto-injector Expert Working Group:

Recommendations to support the effective and safe use of adrenaline auto-injectors

November 2021

Abbreviations

AAI	Adrenaline auto-injector
AC	Anaphylaxis Campaign
ADR	Adverse Drug Reaction
BNF	British National Formulary
BSACI	British Society for Allergy and Clinical Immunology
CCG	Clinical Commissioning Group
CHM	UK Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CMO	Chief Medical Officer
DHSC	Department of Health and Social Care
DSU	Drug Safety Update
EMA	European Medicines Agency
EWG	Expert Working Group
FSA	Food Standards Agency
GP	General Practitioner
HCP	Healthcare Professional
MedDRA	Medical Dictionary for Regulatory Activities
mcg	microgram (one millionth of a gram)
mg	milligram (one thousandth of a gram)
ml	millilitre (one thousandth of a litre)
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
NORA	Network for Online Registration of Anaphylaxis
PIL	Patient Information Leaflet
POM	Prescription Only Medicine
PFD	Prevention of Future Death reports
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
YCS	Yellow Card Scheme

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1 Introduction

Adrenaline auto-injectors are licensed medicinal products that deliver adrenaline by means of an auto-injector device for the emergency treatment of anaphylaxis, a life-threatening severe allergic reaction. Adrenaline auto-injectors are intended for self-administration by a patient, or administration by a carer, and should be carried at all times by patients considered to be at risk of anaphylaxis, so the medicine is available for immediate use, before the arrival of the emergency services. Death from anaphylaxis can occur within a very short period of time and therefore swift intervention by the administration of one or more adrenaline auto-injectors can be life-saving. Adrenaline auto-injectors are critical medicines, their effectiveness being of paramount importance.

1.1 Background to Formation of Adrenaline Auto-injector Expert Working Group

1.1.1 Adrenaline auto-injectors licensed in the UK

Epipen, Jext and Emerade are three brands of adrenaline auto-injector (AAI) licensed in the UK, all of which are available in 150 mcg (0.15 mg) and 300 mcg (0.3 mg) strengths. Emerade is also available in a 500 mcg strength. The labelled strength of an AAI reflects the dose of adrenaline dispensed by the device in a single injection but the amount of adrenaline reaching the bloodstream in a particular time window may differ according to patient-specific and device-specific factors. This is discussed in more detail further on in the report.

Specific instructions for use need to be followed for each brand of AAI, owing to differences in design. It is imperative that patients, and their carers, are familiar with their particular device so it can be used with confidence in an emergency.

The licensed information for prescribers is laid out in the Summary of Product Characteristics (SmPC) and in a more patient-friendly format in the patient information leaflet (PIL). These are available on-line, to all, through the MHRA website https://www.gov.uk/guidance/find-product-information-about-medicines and the electronic medicines compendium https://www.medicines.org.uk/emc/ searchable by product name.

1.1.2 Regulatory background

A Coroner's report in 2010 led to an initial review of AAIs by the MHRA in 2012. Submissions were subsequently made to the Chief Medical Officer (CMO) by the parents of the patient who died, that questioned the adequacy of evidence to support the effectiveness of AAIs, particularly in relation to device-specific factors. At the CMO's request, the MHRA re-opened its review in 2013, the findings from which were considered by the UK Commission on Human Medicines (CHM) in January 2014.

CHM's recommendations following the review included:

- A need for clinical studies in healthy human volunteers to investigate the levels of adrenaline in the bloodstream (the clinical pharmacokinetic - PK – effects) and the effects of adrenaline on the body (the pharmacodynamic – PD – response), following AAI administration.
- A need for improvements to educational materials and product information.

CHM endorsed the existing regulatory advice that patients at risk of anaphylaxis should carry two AAIs at all times.

The MHRA, as the UK's medicines regulatory authority, subsequently sought a Europe-wide safety review into AAIs which led to the following outcomes as legal requirements, as of 14th August 2015:

- Strengthening of prescribing information to support the recommendation for patients to have access to two AAIs;
- The implementation of measures to improve training in the use of AAIs;
- A requirement for marketing authorisation holders (MAH)s of AAIs throughout Europe to conduct clinical studies in healthy volunteers to investigate adrenaline blood levels (PK) following AAI

administration and effects on the cardiovascular system (PD). Studies have been conducted for all devices marketed in the UK and the results reflected in summary form in updates in the product information (principally section 5.2 of the SmPC).

1.1.3 Coroners' inquests

Coroners' inquests into further fatalities from anaphylaxis have served to highlight a range of issues in relation to AAIs. These have included device-related factors that may influence the effectiveness of AAIs; clinical practice in relation to the prescribing and use of AAIs; the availability of AAIs for emergency use in the wider community; and the communication of vital message to patients and other stakeholders in the management of anaphylaxis. The findings from the inquests, reflected in the Coroners' prevention of future death reports, and results from the clinical studies mandated following the European review, were catalysts behind the MHRA's proposal to form an adrenaline auto-injector expert working group (AAI EWG).

2 Adrenaline Auto-injector Expert Working Group (AAI EWG) – scope of work

In October 2019 CHM endorsed the formation of an Adrenaline Auto-injector Expert Working Group (AAI EWG) to examine a range of cross-cutting areas to support the effective and safe use of adrenaline auto-injectors (AAIs) for the emergency treatment of anaphylaxis.

In March 2020 CHM agreed the Terms of Reference and membership of the EWG, drawn from a wide cross-section of stakeholders including Patient Support Groups and representatives of the patient experience; leading allergy and immunology specialists in primary and secondary care, and critical care medicine; leaders from NHS England/NHS Improvement, the Royal Pharmaceutical Society, Community Pharmacists, and the British Paramedic Association.

2.1 Terms of Reference

The Terms of Reference (ToR) were agreed as follows:

1. Recommendations on prescribing and use of adrenaline auto-injectors: effective implementation of these through clear and consistent communications, supported by AAIs in presentations that will accommodate patient needs
2. To consider the feasibility of wider availability of adrenaline auto-injectors in public places.
3. Improved data collection and adverse event reporting.
4. Improved communication channels to convey prompt, accurate information, particularly when matters of concern that require immediate awareness arise.

2.2 AAI EWG meetings held

The AAI EWG met on four occasions by virtual conference between April and July 2020 and their conclusions and recommendations were considered and endorsed by CHM in August 2020. Some additional recommendations were made by CHM. This report provides a combined summary of the conclusions and recommendations of the AAI EWG and CHM, to support the effective and safe use of AAIs.

3 Recommendations of the AAI EWG on the Terms of Reference (ToR)

3.1 Prescribing and use of AAIs (First ToR)

3.1.1 Background

Coroners' concerns set out in Regulation 28 (Prevention of Future Death) notices included a need for better communication of vital messages relating to early administration; availability of two AAIs at all times; and device-specific training. The sufficiency of a 300 mcg dose of adrenaline for patients at high risk of a severe anaphylaxis episode was also questioned. Presentation of AAIs in dual packs to help ensure the availability of two AAIs at all times was suggested and the potential benefit of trainer auto-injectors with needles to more closely mimic an authentic AAI was also raised.

The AAI EWG considered the Coroners' concerns and made a range of recommendations that can be summarised as follows:

3.1.2 Recommendations - early administration of adrenaline

An AAI should be administered early, at the first signs of anaphylaxis, given clear evidence that this improves outcome for patients. This requires the patient and carer to be confident to recognise the early signs of anaphylaxis and to be able to distinguish a severe, life-threatening allergic reaction from one that is less severe and does not require adrenaline. This can be challenging, given the wide range of signs and symptoms of anaphylaxis. If there is doubt about the severity of an episode, adrenaline should be administered without delay as the risks of delay outweigh any potential harm from unnecessary administration of adrenaline.

The mnemonic A,B,C for Airway, Breathing and Circulation is widely used and understood. The placing of anaphylaxis signs and symptoms in these categories can be helpful therefore. It should be emphasised that **just one severe symptom in any of these categories is sufficient to warrant adrenaline.** The presence of milder symptoms alongside should not be viewed as reassuring. It is not uncommon for patients to require a second dose of adrenaline before the emergency services arrive. Again, avoidance of delay is key and a second AAI should be administered **if there is no improvement 5 minutes after the first AAI**. This underlines the importance of having two AAIs available at all times.

The following is a suitable template for advice to give patients and carers:

Because the onset of anaphylaxis can be very fast, an adrenaline auto-injector should be used ***without delay*** *as soon as anaphylaxis is suspected, followed immediately by* ***dialling 999*** *to summon emergency medical help.* ***An auto-injector should be administered, even if in doubt.***
There are a number of possible signs of anaphylaxis (a severe, life-threatening allergic reaction). Any **one** *of the following signs/symptoms is enough to* warrant ***immediate use*** *of an adrenaline auto-injector:*
Airway (A):
•*swelling in the throat, tongue or upper airways (tightening of the throat, hoarse voice, difficulty swallowing)*
Breathing (B):
•*sudden onset wheezing*, *breathing difficulty, noisy breathing*
Circulation (C):
•*dizziness, feeling faint, sudden sleepiness, tiredness, confusion, pale clammy skin, loss of consciousness*
Do not delay *in administering an adrenaline auto-injector if you have* ***any*** of the above signs or symptoms, *even if you also have signs that you would normally associate with a milder reaction (such as an itchy throat or swelling of your lips).* ***Take notice of severe signs and symptoms****, regardless of what else is happening to you.*
If in any doubt about severity, or if previous reactions have been severe, an adrenaline auto-injector should be used. If there is no improvement 5 minutes after the first injection, or if there is a deterioration after an initial improvement, the second auto-injector should be used whilst waiting for the ambulance. Other medicines such as antihistamines and inhalers can be given as necessary.

This advice should be harmonised across products, and between stakeholders that offer advice. Key elements to communicate "when and how" to use an AAI will be incorporated in a prominent, boxed section at the head of the patient information leaflet, going forwards.

Protocols issued to emergency call handlers receiving 999 or 111 calls also need to be robust and consistent, to ensure correct and timely identification of anaphylaxis by the call handler and to provide advice to bystanders as well as patients, while an ambulance is awaited. The protocols should ensure that as soon as anaphylaxis is suspected by a call handler, its immediately life-threatening nature should trigger a Category 1 ambulance response, without exception.

3.1.3 Recommendations - posture of the patient in anaphylaxis

This is frequently under-recognised as a key component of correct anaphylaxis management. There is a clear rationale for the patient to stay lying down, with legs elevated where possible, in order to assist blood flow back to the heart and to vital organs. If patients are struggling to breathe, they may need to sit up but this should be for as short a time as possible. Reliever inhalers, if available, should be given where there is wheezing.

It is imperative to avoid any sudden change in posture and above all, the patient must not be allowed to stand up, or sit in a chair, even if they are feeling better - due to the risk of cardiac arrest. Pictograms should be used where possible to illustrate correct posture and training videos should also reflect this message consistently.

3.1.4 Recommendations - two AAIs should be carried at all times

It should be the norm for patients at risk of anaphylaxis to have two AAIs available to them at all times. This is to meet the potential need for a second dose of adrenaline before the arrival of the emergency services, which is not uncommon. Having two AAIs available does not necessarily mean that patients should receive two AAIs with every prescription, as sometimes only one AAI needs to be replaced. Duo packs (packs of two AAIs) may help to ensure that patients have two AAIs, but single packs still need to be available for occasions where only one AAI needs to be replaced.

3.1.5 Recommendations - training devices and instructions for use

Trainer devices are available from all the manufacturers, on request. Patients and carers are strongly encouraged to obtain these to ensure familiarity with the particular brand supplied as there are important differences in the way each is used. The trainer devices do not contain a needle or adrenaline but otherwise mimic the functionality of a real device. Importantly, trainer devices can be re-used, allowing the patients and carers to practise the action of administration.

Although some patients who are afraid of needles might benefit if trainer devices included needles so they could get used to the sensation, such devices could be used once only and there would be potential risks such as infection and needle stick injuries. Familiarisation of such patients to the sensation of a needle using manual injection using a syringe and needle under medical supervision is a safer option therefore.

Although the different brands of AAI are used in different ways, there are some key principles that are common to all. Where possible therefore, advice should be harmonised but where important device-specific advice applies, this should be clearly communicated. Above all, patients, carers, and healthcare professionals, must be made aware of the need for brand-specific training so patients will be confident to use their particular AAI in an emergency.

3.1.6 Recommendations on labelled strength of AAIs and adrenaline dose

3.1.6.1 Relationship between adrenaline bioavailability and dose

Only one brand of AAI (Emerade) is available in a 500 mcg strength, other brands being available in a maximum strength of 300 mcg.

The strength of an AAI reflects the amount of adrenaline administered per injection but this does not necessarily reflect the amount of adrenaline that reaches the bloodstream (the “bioavailability”), particularly in the early time period following injection which is the most critical period for the patient. The majority of cases of anaphylaxis due to food do not result in death but approximately half of the patients who do not survive, die within 30 minutes after consuming the allergen. Death can occur much sooner than this in anaphylaxis cases associated with insect venom or administration of drug.

Adrenaline bioavailability (levels in the blood) may be influenced not only by the administered dose but also by factors specific to the device and the patient. For example, the amount of adrenaline reaching the bloodstream in the early period may be affected by device-specific factors such as the length of the needle which will affect the depth of penetration of the adrenaline, as well as the force of injection. These factors may in turn influence the degree of contraction of blood vessels (vasoconstriction), a known local

pharmacodynamic (PD) effect of adrenaline, at the site of injection. Blood vessels in the tissue under the skin will also tend to be constricted in the later stages of anaphylaxis when “shock” has set in. This supports the need for early administration of adrenaline before this has occurred, given that vasoconstriction will slow the uptake of adrenaline into the bloodstream.

It was in recognition of this biological complexity that the 2015 European safety review mandated that PK/PD studies should be conducted to investigate adrenaline blood levels and its effects following AAI administration.

3.1.6.2 Pharmacokinetic data following AAI administration

Pharmacokinetic (adrenaline blood level) data are now available for all marketed devices in the UK (Emerade, Epipen and Jext). The data are included in summary form in section 5.2 of the SmPC for all devices. Adrenaline levels in the bloodstream were demonstrated to be overall higher, as a proportion of dose administered, in the first 30 minutes following injection with the higher strength presentations of Epipen and Jext, compared with the Emerade device which has a longer needle. This suggests that needle length may not be the predominant factor affecting adrenaline uptake into the bloodstream and that the force of injection may be important also.

3.1.6.3 Conclusions and recommendations on AAI strength

Although Epipen and Jext are available in a maximum strength of 300 mcg, these AAIs deliver more adrenaline, as a proportion of dose, to the bloodstream in the first 30 minutes following injection, compared with Emerade 500 mcg. Therefore, the development of a 500 mcg strength for all AAIs cannot be recommended at present. Patients can be reassured that a single Epipen or Jext 300 mcg AAI is a suitable replacement for an Emerade 500 mcg AAI. Prescribers should follow the licensed recommendations on dose for each AAI.

Different patterns of adrenaline bioavailability (adrenaline blood levels) between devices, particularly in the clinically important early time period following injection, should be clearly communicated to prescribers and patients. AAIs are prescribed for a patient to carry and use in the event of anaphylaxis. The prescriber therefore needs to make a clinical judgement in advance on the patient’s potential requirement for adrenaline, should anaphylaxis occur. This contrasts with adrenaline administered to treat anaphylaxis in a healthcare setting where dose can be adjusted to clinical need at the time.

3.1.7 Product labelling

Coroners’ concerns have highlighted that it is imperative for the outer packaging of an AAI, storage case and the device itself, to include vital information that can at once be seen and understood by the patient and carer, or a bystander who has stepped in to help, during an emergency.

Going forwards, the following vital warnings will be included on the product such that they will be immediately visible to all concerned in an emergency:

“Administer immediately at the first sign of anaphylaxis. Do not delay”,

“Call 999 for an ambulance stating anaphylaxis (pronounced “ana-fill-axis”).”

“Use your second auto-injector if there is no improvement after 5 minutes.”

“Always carry two adrenaline auto-injectors with you and make sure you know how to use your particular auto-injector.”

3.1.8 Over-arching key messages

The following are key messages that should be conveyed:

What to do in an emergency:

- Use your adrenaline auto-injector **immediately** if you have **any** signs of anaphylaxis. **If in doubt use. Don't delay.**
- **Dial 999** – say anaphylaxis ("ana-fill-axis") – straight after using your auto-injector.
- **Lie down and raise your legs.**
- **Sit up** if you are struggling to breathe but **don't change position suddenly.**
- **Lie down again** as soon as you can.
- **Stay lying down** even if you are feeling better.
- **You must not stand up** even if someone encourages you to.
- **Use your second auto-injector** if you haven't improved after 5 minutes.

Be prepared:

- **Carry two adrenaline auto-injectors** with you at all times.
- You **must use** your auto-injector **as soon as** you notice **any signs** of **anaphylaxis.**
- **Make sure you know beforehand what the signs are** so you can act swiftly.
- Make sure you know **how to use** your auto-injector **before** you need to. **Get familiar with it. Get a trainer auto-injector** from the manufacturer. **Practise.** If you change brand, **get familiar with the new one.** Each one is used differently.

3.1.9 Stakeholders

The recommendations made are pertinent to a range of stakeholders, exemplified by those in the following list. This is not an exhaustive list and will be added to as necessary.

- Patient support groups;
- Marketing authorisation holders
- The National Institute for Health and Care Excellence (NICE);
- The British National Formulary;
- Professional associations of clinical allergy specialists in primary and secondary care, in particular the British Society for Allergy and Clinical Immunology;
- Professional associations in intensive care and emergency medicine, in particular the UK Resuscitation Council;
- Clinical Commissioning Groups and Regional Prescribing Committees;
- Pharmacy professionals in the community and hospital practice;
- Emergency responders including paramedics and ambulance crews;
- Prescribers in primary care such as general practitioners and specialist nurse prescribers;
- Emergency call handlers and those responsible for drawing up clinical algorithms to identify and manage anaphylaxis while an ambulance is awaited;
- Schools and other educational establishments.
- Providers of basic life support (BLS) and advanced life support (ALS) courses.

3.2 Wider availability of adrenaline auto-injectors (Second Term of Reference)

3.2.1 Background

In June 2019, having taken advice from CHM, the MHRA responded to a Coroner's suggestion that AAIs should be made available in public places in much the same way as defibrillators are. The advice was that the risks of such a provision would be likely to outweigh the benefits.

Risks were noted on clinical and quality (pharmaceutical) grounds:

1. The difficulty of distinguishing collapse due to anaphylaxis from collapse due to other causes such as a myocardial infarction (a heart attack) accompanied by a tachyarrhythmia (an abnormal, fast heart rhythm) where the administration of adrenaline could have fatal consequences;
2. Whereas defibrillators possess diagnostic capability that can determine whether, and when in the cardiac electrical cycle, an electric shock should be delivered, AAIs have no such facility;
3. Several technical and practical challenges exist, including:
    - A short shelf-life (time to expiry) of 18 – 20 months means that it is not uncommon for AAIs reaching patients to have around 15 months or less to expiry. If AAIs were made available in public places, they would need regular checks on expiry dates and frequent replacement;
    - Currently available AAIs need to be stored below 25 deg C and must not be allowed to freeze. The susceptibility of i) adrenaline to deterioration at high temperature and ii) the delivery mechanism to temperature extremes, would require storage in a temperature controlled environment. Defibrillators are commonly located outside, often in direct sunlight or in an environment susceptible to freezing. [Whereas AAIs are intended to withstand temperature fluctuations that are inevitable if someone is adhering to advice and keeping their AAIs with them at all times, prolonged storage at temperatures outside the recommended range risks an AAI not functioning as it should do in an emergency.]
    - The administration of AAIs is not intuitive for an untrained individual and particular brands have different instructions for use, according to the device mechanism;
    - Defibrillators, intended to be accessible with ease, are often stored in unlocked cabinets. Their diagnostic capability guards against harm from inappropriate use. AAIs would require secure storage.
4. AAIs are marketed with different adrenaline doses and needle lengths; individual prescriptions take age and body weight into consideration when deciding on the device. Therefore any one device would not be appropriate for all patients.

In response to further calls from patients and clinical allergy specialists to make AAIs more widely available in public places the MHRA proposed that this should be reconsidered, provided safeguards to manage the risks could be implemented. The subject of wider availability was also raised in a petition to parliament to which the MHRA and the Department of Health and Social Care jointly responded.

https://petition.parliament.uk/petitions/258291.

Arising from these ongoing calls from patients and healthcare professionals, CHM endorsed that the subject of wider availability of AAIs should be included as a specific ToR for the AAI EWG.

3.2.2 Recommendations - availability in public places

The AAI EWG discussed wider availability of AAIs and concluded that there are benefits to be gained, especially for those individuals who present with anaphylaxis for the first time in a public place. However, the AAI EWG also recommended that suitable safeguards should be implemented to minimise the risks previously noted by CHM.

Wider availability of AAIs in suitable public places or venues would need to go hand in hand with accredited training, to ensure such devices would be used safely and effectively. This situation prevails in Ireland where any individual, or organisation, can in principle be supplied with an AAI for use in an emergency, provided one or more individuals take responsibility to ensure the safe and effective use of those AAIs, and have undergone accredited training to ensure this. The medicines regulator in Ireland provides a portal where responsible individuals/organisations are listed, with the emergency medicines which they are entitled to hold.

There would need to be further legislative amendment in the UK to enable the potential supply of AAIs that are not issued against a named prescription, other than to educational establishments defined as schools under the Education Act (the current amendment under Schedule 17 discussed below). The extent of any legislative amendment would need to be informed by an exercise to gather information on settings at highest risk of people presenting unexpectedly with anaphylaxis.

The roll-out of accessible training courses will be key to the successful implementation of wider availability. The Patient Support Groups in the UK – the Anaphylaxis Campaign and Allergy UK – have stepped forwards and expressed willingness to lead on this, given their experience already in offering training in anaphylaxis and AAI use.

There are many target groups and locations where wider availability could be of particular benefit such as universities, colleges, youth activity groups, restaurants, gyms, leisure centres, cinemas, and shopping centres. However, any such premises or organisations would need to ensure that AAIs would be acquired responsibly, stored securely and that responsible individuals on-site were trained, to support the safe and effective use of AAIs.

Wider availability of AAIs in public places should not be viewed in any way as a replacement for prescribed AAIs carried by patients but to provide for unforeseen circumstances. Importantly, extension of AAI availability to public places would need to be accompanied by evidence that the AAI supply chain is able to meet the extra demand on an ongoing basis.

3.2.3 Special provision for schools

In 2017, a legislative amendment was made to the UK Human Medicines Regulation under Schedule 17 that allows schools as defined in the Education Act to obtain AAIs without a prescription. AAIs supplied in this way are to be kept on school premises for use in an emergency to treat anaphylaxis, in a pupil known to be at risk. The AAIs held by a school are intended as a back-up and not to replace a pupil's own AAIs. The accompanying guidance issued by the Department of Health specifies that the back-up AAIs are intended for use in children who are medically authorised, and where parental/guardian consent is in place, to receive the backup AAI(s).

There is also provision in the legislation, under Regulation 238, for an emergency medicine listed in Schedule 19 (which includes adrenaline in a formulation and presentation consistent with that in AAIs) to be administered to anyone for the purpose of saving a life. Therefore, a school's back-up AAI, which has not been supplied against a prescription for a named individual, can in principle be used in the event of an emergency to save the life of an individual who develops anaphylaxis unexpectedly. The provision should be reserved for exceptional circumstances only, that could not have been foreseen.

3.2.4 AAIs in healthcare settings

Errors involving adrenaline are among the commonest drug errors reported by emergency responders. The administration of 1:1000, instead of 1:10,000, adrenaline intravenously can be instantly fatal; whereas the administration of 1:10,000 intramuscularly in anaphylaxis is likely to be ineffective. The use of AAIs in place of adrenaline ampoules more widely in healthcare settings might help to prevent this. However, AAI supply

has been fragile and therefore any additional AAI use that could potentially be met by other presentations of adrenaline should be avoided where possible.

The clear labelling of emergency kits to distinguish between cardiac resuscitation or anaphylaxis, with each containing the appropriate concentrations of adrenaline, would also help to avoid error, as would supply of pre-filled syringes (for manual injection). The labelling of adrenaline ampoules as 1:1000 and 1:10,000 adds to the confusion and is not in line with current naming standards for medicinal products. The British Pharmacopoeia (a published collection of quality standards for UK medical substances) is currently considering a revision of adrenaline ampoule labelling to amend the expression of strength and to add the route of administration.

Limited use of AAIs can be justified in some limited healthcare settings but not on a general basis.

3.2.5 Stakeholders

Wider availability of AAIs would require engagement from a wide range of stakeholders and would also require legislative amendment to extend the scope of permitted supply. A robust training programme to support wider availability would also be needed. A public consultation will be undertaken, to inform a hierarchy of need and feasibility which will in turn help to inform any legislative amendment required and the training allied to this. A number of preparatory steps are therefore required.

Stakeholders will include the following and will be added to as necessary :

- The Anaphylaxis Campaign and Allergy UK (as lead providers of accredited training courses to support wider availability)
- The Food Standards Agency – to target restaurants and other eating establishments;
- Government departments responsible for venues such as leisure and sports facilities; cinemas, theatres and other entertainment venues; transport hubs such as airports; youth activity clubs and camps; further and higher education establishments; social care settings including residential facilities; prison and hostels for the vulnerable.

Stakeholders identified as key to the safe deployment of adrenaline in emergency kits in the healthcare setting:

- The British Pharmacopoeia (adrenaline labelling)
- NHS England and NHS Improvement

3.3 Improved data collection and adverse event reporting (Third Term of Reference)

3.3.1 Background

The third ToR on data collection and adverse event reporting arose from an acknowledgement by CHM of deficiencies in data collection relating to anaphylaxis incidents as well as data on AAI usage (use in an anaphylaxis episode rather than prescribing figures).

Deficiencies in AAI adverse event reporting were recognised by the AAI EWG, with current reporting not being adequate to distinguish between device malfunction and a failure to respond to adrenaline that had been delivered as intended.

The need to obtain more robust data on device usage was also recognised so that more reliable estimates of the number of AAIs, in which brands, are needed for successful treatment of anaphylaxis. Accurate information on device usage is also important to inform risk of device malfunction as a proportion of devices actually used, rather than sold. This will in turn assist prompt signal detection should the possibility of a device defect emerge. Given that the vast majority of AAIs carried by patients are never used and therefore not put to the test, adverse event rate expressed as a proportion of devices sold can be misleadingly low.

As a complement to spontaneous reporting, the potential value of solicited adverse event monitoring, to prospectively acquire data on AAI deployment and its success or failure to treat anaphylaxis episodes, was also acknowledged.

3.3.2 Terminology for device-related adverse events

The terminology for reporting and classifying adverse events is outlined in the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA included a variety of device-related terms for reporting incidences, however, MedDRA did not include an autoinjector-specific term, which could lead to inconsistencies in reporting, considering that adrenaline is available in various presentations. The EWG endorsed the addition of a term relating to autoinjector activation failure to MedDRA.

The request was submitted to MedDRA for consideration and has resulted in the addition of 'autoinjector activation failure' as a lower level term (LLT) within the dictionary. The addition will enable easier identification of autoinjector activation failure reports when investigating potential product defects. The new term is present in MedDRA version 23.1, released in September 2020.

Inconsistencies in the terms currently being used to report adverse events and device issues were also noted. To improve consistency of reporting, the marketing authorisation holder will be asked to classify reports with the following terms:

- 'Autoinjector activation failure' should be used to classify any incidence of the AAI failing to activate.
- 'Drug ineffective' should only be classified if the device activated and adrenaline was administered but was then considered ineffective
- If the device didn't administer the adrenaline (whether it activated or not), 'drug dose omission by device' should be classified in addition to the 'device failure' term.
- If the case includes a suspected device handling error, this should also be classified using the term 'device use error'.

3.3.3 Solicited reporting of device-related adverse events with AAIs

The reporting of device-related incidents such as failure of the auto-injector to activate is important in monitoring the safety of AAIs and ensuring they are functioning as intended. To do this, it is important to encourage the reporting of device-related incidents as well as ensuring that the AAI is retained so that the root cause of the incident can be investigated, which in turn provides information as to whether the issue could affect other AAIs across the batch or product line.

The majority of spontaneous reports received by the MHRA regarding device-related incidents are received indirectly via the marketing authorisation holder, rather than directly from patients or carers. In many of these reports, the AAI has already been disposed of, meaning further investigation is not possible. Solicited reporting is considered a way of targeting specific groups to increase the number and quality of reports, while also increasing the chance of the AAI being retained for further investigation.

Ambulance service personnel are often the first to interact with a patient following anaphylaxis, with patients instructed to call an ambulance following use of an AAI; therefore, the ambulance service was identified as a key group to assist with targeted solicited reporting. Previous reports have suggested that used AAIs are often retained by the ambulance service for safe disposal. Paramedics are therefore well positioned to collect precise details of any device-related issues directly from the patient as well as being in a position to retain any AAI device that has not functioned correctly so that further investigations can be carried out.

3.3.4 Improving data on the usage of AAIs

There is currently a lack of accurate information on AAI usage, which makes it difficult to estimate the frequency of adverse events and device issues. Frequency rates are currently calculated using the number of AAIs prescribed, which provides an overly reassuring event frequency as this assumes all AAIs are used.

In reality, as AAIs are only used for emergency treatment of anaphylaxis, the majority remain unused and are replaced when the AAI expires.

Databases that are used to estimate usage, including Clinical Practice Research Datalink (CPRD) and IQVIA MIDAS, are unable to provide an accurate estimate of AAI usage as they base the estimate on the assumption that all of the prescribed medicine is used by the patient, which for AAIs is not the case. There is therefore a need for alternative sources of data on AAI usage.

A survey of patients, conducted through the patient groups (Allergy UK, Anaphylaxis Campaign) is considered a potential means of obtaining data on AAI usage. While some limitations such as patient recall and selection bias are identified, a patient survey would allow the collection of data on usage directly from users of AAIs, who will know whether they have needed to use their AAI for anaphylaxis. A patient survey will provide valuable information on the number of AAIs used compared to the number prescribed.

Registries provide a longer term method of collecting data on the usage of AAIs. There is currently a European anaphylaxis registry, run by the Network for Online Registration of Anaphylaxis (NORA). However, the registry does not have any participating UK centres. The Food Standards Agency (FSA) issued an invitation to tender for the establishment of an anaphylaxis register. The tender has been won by a UK centre that is exploring linking this new registry to the existing NORA registry. Collaborating with the FSA to ensure that the registry is able to collect data on AAI usage would provide a valuable new source of data on AAI usage.

The UK's fatal anaphylaxis registry has not been maintained for some years due to a lack of resource. A comprehensive, in-depth fatal anaphylaxis registry of UK cases would be a highly informative resource on many aspects of anaphylaxis including usage of AAIs in relation to outcome. Therefore, the re-establishment of a fatal anaphylaxis registry in the UK is also recommended.

3.3.5 Stakeholders

Stakeholders able to assist in improved data collection and adverse event reporting are likely to include the following, with additional stakeholders involved as necessary:

- Patients, carers and prescribers
- Marketing authorisation holders and qualified persons for pharmavigilance reporting to ensure compliance with adverse event reporting using updated terms
- Paramedics and the ambulance service to assist with solicited adverse event reporting and retention of potentially defective devices
- Patient organisations to assist with a patient survey on AAI usage
- Food Standards Agency to collaborate on an anaphylaxis registry to ensure collection of data on AAI usage
- The British Society for Allergy and Clinical Immunology – towards the establishment of a fatal anaphylaxis registry

3.4 Improved communication channels (Fourth Term of Reference)

3.4.1 Background

The fourth ToR on communication channels was recognised to underpin all the ToRs, so that patients, healthcare professionals and the wider public can be better informed and therefore equipped to understand the importance of AAIs as a potential life-saving medicine, particularly if AAIs are to be made more widely available which will require more widespread public engagement.

3.4.2 Communications campaign

Central to the campaign is the recognition of the need for patients, carers and healthcare professionals (HCPs) to be informed of key, consistent messages to support the safe and effective use of AAIs. Messages should be simple and clearly conveyed.

Evidence of change in behaviour and improved patient understanding are considered to be markers of a successful campaign. Improved quality of life such as greater confidence to enjoy leisure pursuits would be an important outcome. Patient support groups will be key to informing the campaign and in providing feedback. A reduction in deaths relating to anaphylaxis could be seen as the ultimate marker of a successful campaign.

A communications campaign will ensure that key stakeholders identified to take the recommendations forwards remain engaged with any future developments relating to AAIs. A communications campaign will harness a range of media from social media to direct involvement of key influencers in society. Digital communications will be key to any future campaign.

The development of a communications campaign was paused due to the ongoing pandemic, recognising that behaviours at present are not typical. Once social behaviour has resumed some semblance of normality, the communications campaign will commence.

A communications campaign will aim to dovetail with one proposed by the Food Standards Agency that is specifically concerned with issues around food allergies. There are nonetheless significant areas of overlap in relation to the prevention and management of serious, life-threatening allergic reactions.

4 Implementation of the recommendations

MHRA will communicate the key recommendations endorsed by the Commission on Human Medicines to stakeholders so that these can be acted upon in a timely and coordinated manner. Some actions are already underway such as changes to product labelling to implement key warnings. Other actions will take longer to implement – in particular wider availability of AAIs - which will require legislative consultation and amendment, as well as wider public consultation to ensure that key stakeholders are fully engaged and adequately prepared before roll-out of wider availability.

Members of the expert group have expressed willingness to continue to provide ongoing advice in relation to AAIs, which will continue to be of great value to patients and the wider public.

The Commission on Human Medicines' Adrenaline Auto- Injectors Expert Working Group

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