1. The dark adapted red flash ERG extended protocol.

2. Scope and applications

The ISCEV ERG Standard [1] describes a minimum protocol to test rod and cone system function in the outer and inner retina. This extended protocol proposes the inclusion of red flashes under dark adapted (DA) conditions. The DA red flash ERG can be used to distinguish the function of DA rod and cone systems and can help determine the origins of abnormalities seen in the Standard flash ERGs which may be important for accurate characterization of retinal function and to establish some diagnoses.

It is well established that the normal cone system contributes to the full-field ERG under DA as well as light adapted (LA) conditions. This occurs in DA ERGs evoked by flash strengths greater than 0.1 $cd.s.m^{-2}$,[2] including the ISCEV standard DA 3 ("combined rod cone") and DA 10 ("strong flash") ERGs. Early investigations revealed the contribution of DA cones in the ERG waveform by using colored flashes that exploited differences in the spectral sensitivities of rods and cones [3-5]. These studies showed that the DA ERG waveform to a red flash has two positive peaks. The first, named the x-wave, occurred within 30-50ms and was attributed to DA cone activity. The x-wave was followed by a rod-mediated b-wave [3]. The x-wave is larger than the b-wave during the early stages of dark adaptation when the rod system threshold is high. As dark adaptation proceeds the x- and b-wave amplitudes become similar and finally the b-wave exceeds the x-wave [6].

The DA red flash ERG has several clinical applications and circumstances and diagnoses that may benefit from testing are outlined below:

a) The DA red flashes are usually well tolerated by patients of all ages, and the test is therefore useful if photophobia or photo-aversion confounds the recording of standard LA ERGs. This can occur in the presence of cone dysfunction, but also for example in the presence of media opacity or strong Bell's phenomenon.

c) In cases of generalized cone system dysfunction such as rod- and S-cone monochromacy and cone dystrophy, the DA red flash ERG x-wave may be undetectable, markedly attenuated and/or delayed[7-9].

c) In cases of generalized retinal dysfunction the relative involvement of the DA red flash ERG x-wave and b-wave may suggest predominant dysfunction of cone or rod systems, not always obvious by comparing standard DA and LA ERGs.

d) In cases of severe or selective rod dysfunction the DA red flash ERG can help determine the causes of abnormal or residual DA bright flash ERGs. This occurs for example in vitamin A deficiency [13], fundus albipunctatus (RDH5-retinopathy) [10, 11] and Oguchi disease (SAG- or GRK1- retinopathy) [6] and in some cases of rod-cone dystrophy including early stages of Bothnia dystrophy (RLBP1-retinopathy). In these disorders the DA 3 and DA 10 ERGs have reduced a-waves indicating rod photoreceptor dysfunction, but there may also be reduction in the b:a ratio. The reduced b:a ratio may arise from strong stimulation of the relatively preserved DA cone system, analogous to the photopic hill phenomenon, and produces a b-wave which resembles the waveform of the x-wave.

e) “Bradyopsia” (RGS9- and R9AP-retinopathy). The DA red flash ERG is normal, but LA cone-mediated ERGs are extinguished by repetitive flashes [9, 10]. The combination of a preserved DA red flash ERG x-wave and undetectable or severely abnormal standard LA ERGs is pathognomonic for the disorder.

e) The red flash ERG has been used to detect color vision deficiencies and has been reported to be absent [8, 12] or subnormal [9] in protanopia. The implication is that around 1/100 males would have an absent red flash ERG although this has not been established for an ISCEV DA red flash ERG extended protocol.

3. Identification

Red Flash ERG v5 061117 Corresponding author: Dorothy A Thompson.

Co-authors: Kaoru Fujinami, Ruth Hamilton, Ido Perlman, Anthony G. Robson

4. Patient population

Patients of all ages, referred for investigation of possible retinal dysfunction, retinal dystrophy, generalized cone or rod system dysfunction or patients with photophobia may benefit from the DA red flash ERG, embedded within the ISCEV standard full-field ERG protocol.

5. Technical issues

The DA red flash ERG will follow the specifications of the current ISCEV standard full-field ERG and for most applications may be embedded within the standard protocol [1]. Additional considerations include the following:

a) The spectral characteristics of the red flash. Both peak wavelength and bandwidth may affect the DA red flash ERG. Physical filters e.g. Kodak Wratten filters 26 (dominant wavelength 619nm) or 29 (dominant wavelength 630nm) were used in many older studies, but have been largely superseded by LEDs e.g. peak wavelengths 635nm or 655nm It is noted that peak wavelengths shorter than 620nm may be perceived as orange and that for wavelengths longer than 650nm, waveforms have been reported with a third positive wave, later than the rod b-wave [6].

b) The units of flash strength. The relative (effective) strength of a colored flash depends upon the adaptation and hence spectral sensitivity of the eye. Absolute measures are radiant energy, but for uniformity of clinical use and consistency with other flash stimuli, it is suggested to use photometric units defined in phot cd.s.m^{-2}.

c) Duration of dark adaptation. The choice of dark adaptation duration and flash strength depends upon one of three aims (Figure 1):

i) To isolate the cone-mediated x-wave (peak time 30–50ms): short dark-adaptation of around 5 minutes reveals the x-wave before it is masked by full development of the later rod-mediated b-wave [6, 7, 13].

ii) To separate the x- and b-wave peak times: if an ISCEV Standard period of at least 20 minutes dark adaptation is used, weaker red flash strengths of around 0.03–0.3 cd.s.m^{-2} allow maximum separation in time of the cone- and rod-mediated components.

iii) To match the amplitudes of the DA red flash ERG b-wave with the ISCEV Standard DA 0.01 ERG (rod ERG) b-wave: stronger red flashes have been used. This red flash strength may be subject and age specific if defined in this way e.g. [17]. Further subtraction analysis is beyond the scope of this proposal and can be problematic e.g. [18].

d) Frequency of red flash presentation. The inter-stimulus interval will influence the light adaption of the retina and shape of the DA red flash ERG waveform [14]. A flash rate of 1 per s does not result in diminishing ERG amplitudes [19], but the effects of faster flash rates are not fully established and require further investigation. The ISCEV standard for the DA 0.01 ERG is greater or equal to 1 flash every 2s and a similar frequency may be appropriate for flash strengths that elicit responses of similar amplitude to the DA 0.01 ERG.

6. Calibration

Calibration is in accordance with the ISCEV ERG standard [1]. A spectral photometer is required to determine the spectral characteristics of the red flash. Stimulators may use different combinations of LEDs for different flash strengths, so equal spectral characteristics should not be assumed.

7. Protocol specification

Patient preparation follows that for the current ISCEV ERG Standard [1] and the DA red flash ERG may be embedded within the standard ERG protocol. The following additional specifications are suggested.

a) Stimulus wavelength. For routine diagnostic applications an LED with a peak wavelength of between 635nm (figure 1) and 650nm is suggested to allow separation of x- and b-waves. If Xenon flashes and filters are used it is suggested to use a dominant wavelength of 619nm (e.g. Wratten 26) or 630nm (e.g. Wratten 29). The peak wavelength and bandwidth of the stimulus and method of generation (optical filter or LED), should be stated.

b) Flash strength. It is suggested that a red flash strength of 0.3 cd.s.m^{-2} is included. This has been commonly used. This does not preclude the recording of additional red flash ERGs (ranging around 0.3 cd.s.m^{-2}, see figure 2, to account for age, pupillary dilatation etc), but care should be taken to avoid light-adapting the retina and it may be necessary to increase the inter-stimulus interval. If the red flash stimulus is defined according to that required to elicit a DA red flash ERG b-wave of equal or similar amplitude to the DA 0.01 ERG, this should be acknowledged and the corresponding flash stimuli stated in cd.s.m^{-2}.

c) Duration of dark adaptation. A stimulus strength of 0.3 cd.s.m^{-2} may be incorporated within the ISCEV Standard ERG protocol, after a minimum of 20 minutes DA and after the DA 0.01 ERG. There may be specific reasons for recording the DA red flash ERG after shorter periods of DA (see section 5c; also to minimize the overall recording time), but care should be taken to avoid significant light adaptation prior to the DA ERGs. Mesopic cone-rod interactions associated with shorter DA may increase the variability of the DA red b-wave amplitude.

d) Frequency of red flash presentation. A flash rate of or between 0.5 and 1 per s is suggested,(i.e. an inter-stimulus interval 1 flash every 2 seconds), but longer inter-stimulus intervals may be needed for stronger red flashes. A maximum rate of 0.5 per s conforms to the current ISCEV Standard for the DA 0.01 ERG.

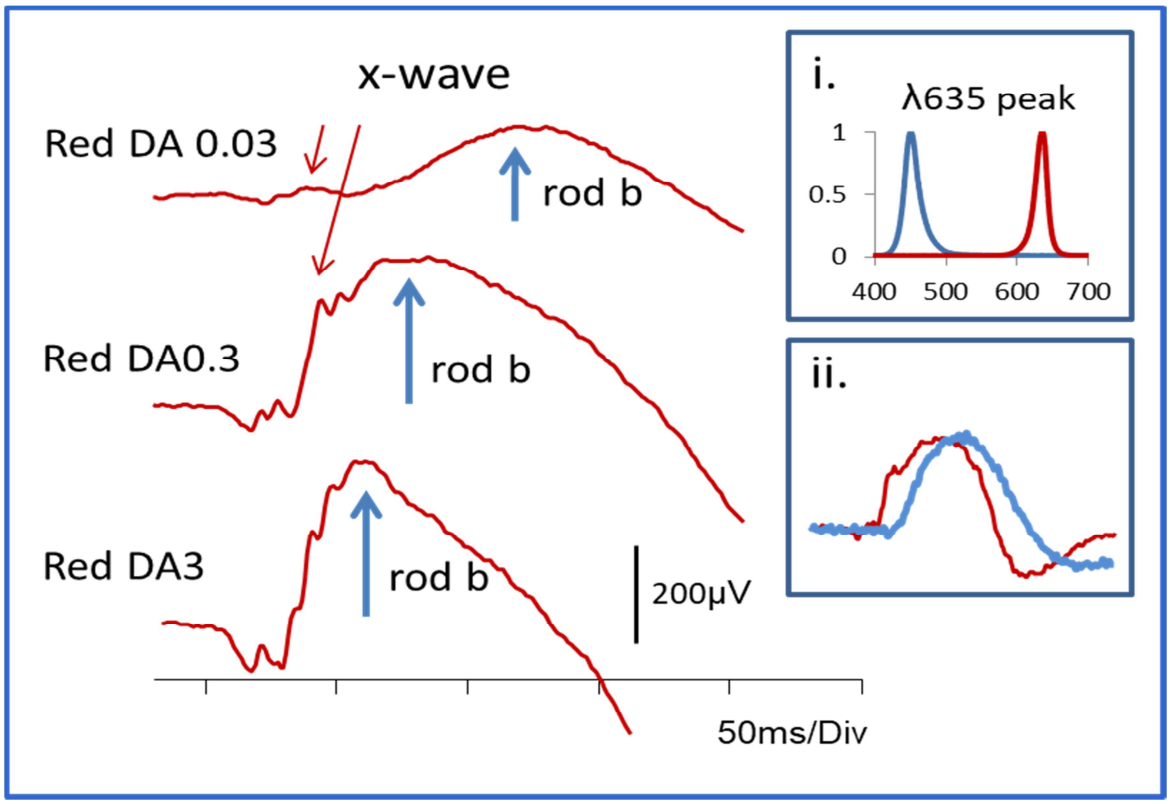

Figure 1: the change in DA ERG waveform to three red flash strengths is shown after 20 minutes dark adaptation from a Caucasian patient. Note the separation in peak time of the x-wave and b-wave to dim 0.03 cd.s.m^{-2} flashes, the enlargement of the x-wave to 0.3 cd.s.m^{-2} and the merging of x- and b-waves at DA 3 in a control subject. Insert i. shows the spectral characteristics of the red and blue LEDs in the Ganzfeld. Insert ii shows the DA red flash ERG to 0.3 cd.s.m^{-2} in a second subject compared with a DA blue flash ERG of 'scotopically matched' b-wave amplitude, in this case DA blue 0.0003 cd.s.m^{-2}. DA red ERGs shown in red, DA blue flash ERGs shown in blue.

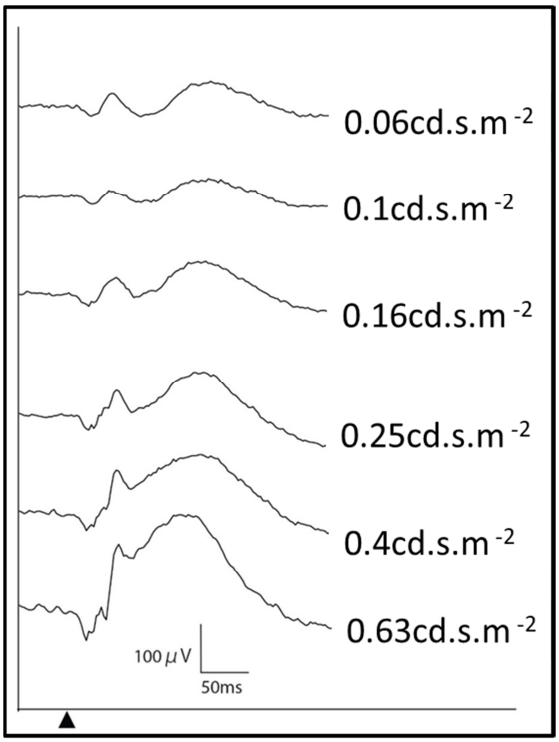

Figure 2. DA red flash ERGs are shown to a range of flash strengths that includes 0.3cd.s.m^{-2}, recorded from a Japanese patient after 20 minute DA λ650nm.

8. Response evaluation

Examples of the DA red flash ERG waveforms are shown in figure 1 for different flash strengths delivered using an LED (peak wavelength 635nm; bandwidth as shown). It is suggested that the DA red flash ERG parameters are noted as follows: a-wave (if present): earliest trough, amplitude relative to baseline, peak time relative to flash midpoint: x-wave: peak or shoulder, amplitude relative to baseline or a-wave trough (if present), peak time relative to flash midpoint: b-wave: peak following x-wave, similar to DA0.01 (rod) ERG b-wave, amplitude relative to baseline or a-wave trough (if present), peak time relative to flash midpoint.

9. Reporting

Reporting the DA red flash should follow the recommendations of the ISCEV ERG protocol. The flash stimulus characteristics (LED or filter), peak wavelength or filter specification (e.g. Wratten 26 or 29) should be stated. The flash strength should be stated. Unless already embedded within the ISCEV standard ERG protocol, pupil size and duration of dark adaption should be stated. The amplitude of the a-wave, x-wave and b-wave and their respective time to peaks may be reported along with age-appropriate laboratory reference data. It is acknowledged that in studies involving ISCEV standard ERGs it may be sufficiently informative to describe the relative reduction or preservation of x-wave and/or b-waves relative to each other and normal values.

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Part B. Justification for the protocol details and description of the consultation process

A systematic review of stimulus parameters and uses of the DA red flash ERG are summarized and tabulated below, with a second table summarizing some of the parameters currently in use by ISCEV members. Feedback was incorporated following presentation of the draft protocol at the BriSCEV eptember 2017 and ISCEV October 2017.

Our review highlights two evidence gaps:

1) Which LED red flash strengths are optimal for different durations of dark adaptation, to visualize the x-wave and maximize the diagnostic utility of x- and b-waves.
2) What happens to the DA red flash ERG in protanopia produced by the suggested extended protocol.

REVIEW OF EVIDENCE

Published specifications are tabulated below (Table1). In summary, red flash strengths range between 0.05, 0.1 [15], 0.5 [16], 0.17cd.m^{-2} [17], 0.25 [18], 2.37 [19], 2.4 [2], 1.5 and 2.5 cd.s/m^2 [20] at 20 minutes DA. When Grass strobes have been used to deliver the red flash the range of intensity settings 1, 4, 8 and 16 have been used, e.g. gr4 white PS22 ~ 3.7 x10^5 candles [7] or gr4 + Wratten 26 filter = 0.02 Log µJoule/cm^2-steradian [21]. Sometimes no numerical value, nor wavelength, is stated: some studies reporting clinical use of the red flash ERG describe flash strength "such that in a normal subject the amplitude of the rod component to the red flash is equivalent to that of the rod-specific response to a dim white flash (dark-adapted 0.01 cd s m-2)", without providing a value [22-25]. Others suggest the red flash luminance is empirically set to achieve ~200µV amplitude scotopic b-wave [26].

TABLE 1 Published stimulus details are tabulated, where available indication of normal response are stated or derived from published figures.

data	Peak λ	Flash strength	DA duration	LED/Xenon
[6] Auerbach & Burian 1955	Wratten 29 635nm Wratten 70 650nm	6 & 12 cd.s.m^{-2}	5 mins	Xenon @30cm
[8] Francois et al 1956	Neon 570 nm	0.1 Joule		Neon 0.2s (orange)
	x-wave 25-60uV@40ms			
[27] Iiyami & Yamaguchi 1990	Wratten 29 blocks below 600nm	86-112cd.s/m^2	30 minutes	
[9] Kellner & Foerster 1992	Wratten 29 623nm	?not stated		Xenon in Ganzfeld
[28] Lovasik et al 1992	Wratten 26 >600 nm	2.37 cd.s.m^{-2}	Not stated	Xenon in Ganzfeld
From figure		90uV@50ms		
[17] Mizunoya et al 2001	LED 660nm	0.17 cd.s.m^{-2}	20 minutes	C/L ganzfeld
[14] Verdon et al 2001	Wratten 26 >600 nm			Xenon Ganzfeld
From figure		@40ms		
[2] Lim and Ohn 2005	Wratten 26 =605nm (Scot match -14Db blue)	2.4 cd.s.m^{-2}	45 minutes	Xenon Ganzfeld
Control data		172.4µV@46ms		N=52 adult
[21] Weleber 1981	Wratten 26 >600 nm	Gr1, 4 and 16	30 mins	Xenon in Ganzfeld
Control data	BA C/L	gr1 = 50µV (25-75) @40-50ms gr4 = 150µV@50ms		N=24 adult

		gr16 = 325µV (200-400) @ 50ms		
[7] Kriss et al 1992	Grass red peak 670nm	Gr4	5 minutes	Grass @30cm
Control data	Skin electrode	14.3 (SD4.9) µV@ 40.4ms (SD2.6) lower limit 4.5µV @46.9		N=30 over 5m and adult
[18] Chen et al 2015 abs	Espion colour dome 635nm	0.25 cd.s/m2	20 mins	LED
Control data	a-wave x-wave b-wave	17.6µV@19.8ms 64.0µV@50.7ms 68µV@72.9ms		N= 37 adult
[13]Hamilton & Graham 2015 abs	Skin electrode	1.5 cd.s/m2	20 mins	N=16 adults
Control data	DA 1.5 cd.s/m2 scotopically matched DA 0.01 rod b-wave 1-5 mins better defined X-wave			

Of interest, the DA red flash ERG to different λ of the filters were investigated in early studies and using a very deep red, Wratten 70, (> 650nm), produced a third positive wave, later than the rod b-wave which has been regarded as specific for chromatic red flash [6], seen also in 660nm red flash figure of [17].

TABLE 2. Specifications used by ISCEV members - Personal communications

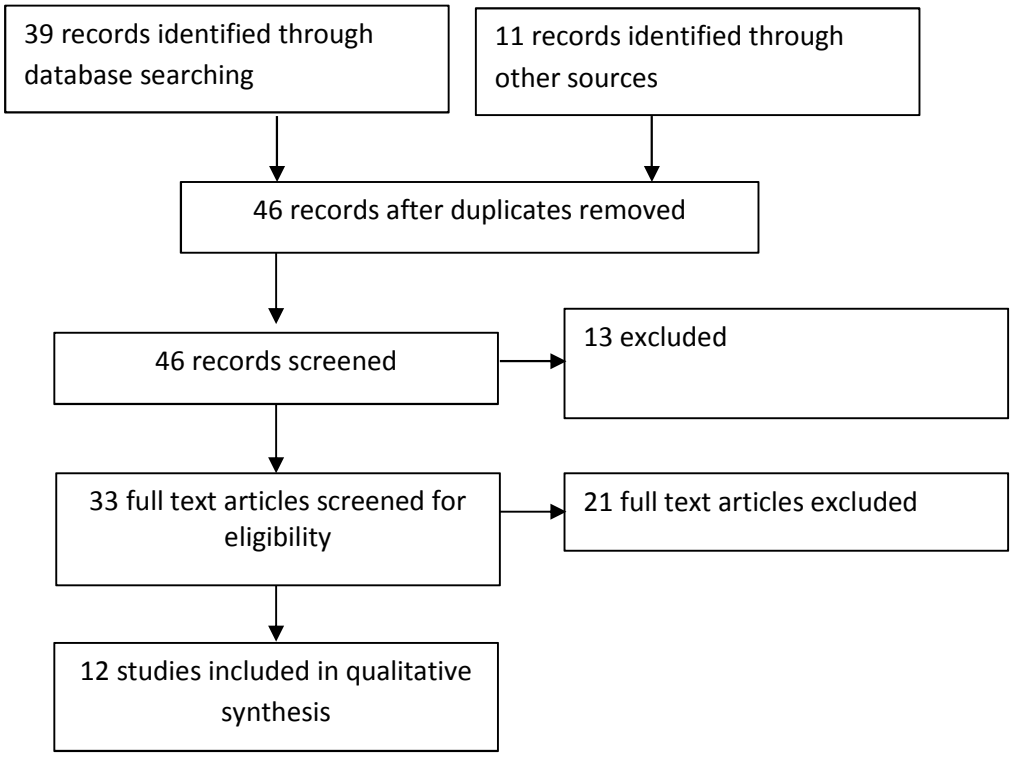
ISCEV LABS	**Peak λ**	**Flash strength**	**DA duration**	**LED/Xenon**
GOSH UK	635nm	0.3 and 2.25 cd.s.m^{-2}	20 mins	LED
MEH UK	645nm	0.2 & 0.3 cd.s m^{-2}	20 mins	LED
JAPAN MIE& NISO	650nm	0.06 & 0.40 cd.s.m^{-2} range 0.06-20 cd.s.m^{-2}	20 mins	LED
	Watts/steroradian/m2/nm (-1.6, -1.2, -0.8, -0.4, 0, 0.4, 0.8, 1.3 log cds/m^2)			
GOSH scot match to 0.01 b-wave Control data	a-wave: b-wave: 8-13 yrs	16uV@49ms median (5th-95th 37-92uV@13-29ms) 305uV@52ms median (5th-95th 179-650uV@45-72ms)		

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29] when writing this report. The search strategy aimed to identify reports of scotopic red flash ERGs in order to extract stimulus parameters of wavelength, flash strength, stimulus duration, temporal frequency, dark adaptation period and amass evidence of its clinical application and range of response expected in normal and clinical cases.

A systematic literature review was performed to find publications that reported the scotopic red flash ERG from the period January 1942 to 10/04/2017 using Medline, EMBASE and Cochrane reviews. The search strategy is shown in appendix 1. Exclusion criteria were animal studies and absence of any stimulus specification.

Data Collection

The search resulted in 39 items that were exported to Endnote XI. A further 11 items were identified and after duplicates were removed, 46 papers were screened. 30 were eligible for further review and underwent full review, after which 21 were excluded, mostly because they mentioned red flash without any stimulus specification of flash strength or wavelength or because the dark-adapted cone ERG a-wave was mentioned without discussing x- or b-wave.



APPENDIX 1 Search strategy

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2. ganzfeld.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
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4. full field ERG.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. full field stimul*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. exp retina cone/ (4073)
7. cone.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
8. cone photoreceptor.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
9. red flash.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
10. x-wave.mp. [mp=title, abstract, heading word, drug trade name, original title, device

manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

11. 1 or 2 or 3 or 4 or 5

12. 6 or 7 or 8

13. 9 or 10

14. 11 and 12 and 13

15. limit 14 to human

285