Technoleg Iechyd Cymru
Health Technology Wales

HEALTH TECHNOLOGY WALES (HTW) EVIDENCE SUMMARY 017 (March 2020)

Virtual reality interventions for the management of pain associated with medical procedures

HTW Assessment Group decision

HTW undertook an evidence review to address the following question: what is the clinical and cost effectiveness of virtual reality (VR) as a distraction therapy for the management of procedural pain? Randomised trials of VR in a range of different clinical settings were identified, and used to estimate the effect of VR on pain during medical procedures. However, the evidence identified comes from use of commercially available VR systems, and we did not identify any VR systems that are CE marked as medical devices for distraction therapy in order to minimise pain associated with medical procedures.

The HTW Assessment Group concluded that there are uncertainties regarding the regulatory approval of VR systems for use in the management of procedural pain, and given these uncertainties, HTW guidance should not be produced at this time. Therefore, this topic will not progress to Appraisal Panel and will not receive HTW Guidance recommendations. The HTW Assessment Group urge any manufacturer of VR systems intended to be used for the management of pain associated with medical procedures to seek relevant regulatory approval. If and when devices with relevant regulatory approval are available, this topic will be revisited.

Why did HTW appraise this topic?

Common medical procedures often induce excessive pain, anxiety and distress to patients undergoing them. Example include wound care, dressing changes, physical therapy for burns, dental treatment, chemotherapy, intravenous access, and labour. Pharmacological interventions can be used to minimise procedural pain, but these can have disadvantages, such as imprecise titration, narrow therapeutic windows, side effects, high costs and potential for drug misuse.

Distraction therapy (for example, exposure to music or video) is an alternative strategy for pain management during medical procedures associated with excessive amounts of pain. VR is another method of delivering distraction therapy to manage pain during procedures.

We searched for studies that compared immersive VR as a method of pain management to standard of care: depending on the condition, this could include pharmaceutical analgesia, anaesthesia, alternative methods of distraction, or non-immersive VR. We included studies irrespective of the content displayed in the VR intervention, method of delivery or the level of immersion achieved by the different VR systems. We extracted data from relevant studies on any pain-related outcomes (usually pain intensity), and also outcomes related to anxiety/distress, procedure completion outcomes such as time required and success rate, quality of life, resource use and adverse events.

Evidence Summary

HTW identified 40 RCTs (covering a population of 2501 patients) and used these to carry out meta-analysis on the effect of VR on pain-related outcomes during medical procedures. The results indicated that VR distraction therapy was more effective than usual care in reducing pain during or immediately after the procedure. The trials included in the analysis covered a range of different medical procedures. Subgroup analysis showed that regardless of the medical procedure the VR intervention shows a positive effect on pain outcomes. Similarly, subgroup analysis showed VR had similar levels of effectiveness in adults and in children. We also looked for evidence of any adverse events associated with using VR in this way: nausea was very infrequent and mild and no other adverse events were reported. However, statistical analysis uncovered evidence suggestive of publication bias in the available evidence. The methods of measuring pain used in the trials also pose difficulties in translating the results into clinically significant changes in pain. The trials identified used commercially available VR systems, that that are not explicitly covered by medical device regulations. We did not identify any trials that used a VR system that is CE-marked for use as a medical device for the management of pain associated with medical procedures, nor are we aware of the existence of any such devices.

No economic evidence was identified on the use of VR distraction therapy in people at risk of pain cause by medical procedures. VR used in this way has the potential to be cost saving if it shows demonstrable reductions in opioid utilization and/or hospital length of stay. However, we did not identify any evidence on how the use VR influences these outcomes.

Evidence Appraisal Report 017 follows, and gives a full report of the evidence on this topic.

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Health Technology Wales

Evidence Appraisal Report

Virtual reality interventions for the management of pain associated with medical procedures

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: what is the clinical and cost effectiveness of virtual reality (VR) as a distraction therapy for the management of procedural pain?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of identifying the best published clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Medical procedures often induce excessive pain, anxiety and distress to patients undergoing routine or specialised care. Common medical procedures that require pain management include wound care, dressing change and physical therapy for burns, dental treatment, chemotherapy, intravenous (IV) access, and labour. The majority of procedures employ suitable pharmacological approaches to minimise procedural pain; nevertheless, these have significant drawbacks, including imprecise titration, narrow therapeutic windows, adverse side effects, high costs and potential for drug misuse (Chan et al. 2018). The inappropriate management of acute pain that results from medical procedures could be accompanied by extended hospitalisation periods with associated short and long-term costs and it also represents a risk factor for the development of chronic pain (Georgescu et al. 2019). Aside from pharmacological approaches to reduce or minimise the pain associated with medical procedures, distraction therapy (for example, exposure to music or movies) is an alternative strategy for pain management during medical procedures associated with excessive amounts of pain.

3. Health technology

Virtual reality (VR) is an artificial 3-dimensional (3D) environment experienced by a person through sensory stimuli, including visual, auditory and often touch. Visually, VR experiences are delivered by a head-mounted display (HMD) that projects stereoptic 3D imagery and tracks head motion in order to allow the users to move naturally around the virtual space. Audio is also usually simulated in 3D through a head-related transfer function which enables the HMD wearer to locate simulated sounds at their real location in the virtual space. Coupled together, the visual and audio

experience creates a sense of immersion or presence for the user within the 3D virtual world (Garrett et al. 2014).

VR was originally developed as a tool for military training and entertainment. Over the past two decades VR interventions have been increasingly applied in healthcare, including in the treatment of phobias and anxiety disorders, cognitive and physical rehabilitation, acute and chronic pain management, support for patients with cancer for hospitalisation and chemotherapy, treatment of eating disorders and obesity, surgical training and aid in surgical planning and performance (Indovina et al. 2018). In clinical practice, the use of VR was most frequently studied as a means of attenuating pain perception, anxiety and general distress during painful medical procedures, such as wound care, dental procedures or other routine medical procedures (Li et al. 2011).

VR shows a promising alternative to traditional interventions for enhancing the effectiveness of distraction for acute pain. It is speculated that within a clinical setting, VR could potentiate and possibly replace standard pharmacotherapy for acute pain in order to address the growing epidemic of prescription narcotic dependence and misuse (Pourmand et al. 2017). The immersive and multi-sensorial experience coupled with the possibility of active exploration of virtual environments could facilitate the shift of attention away from the experienced pain stimuli and re-shape pain perception in medical care settings (Georgescu et al. 2019). In addition to the distraction therapy, VR displays block the real and distressing scenes in medical practice, and thus, the intervention simultaneously diverts the negative stimuli associated with medical procedures (Luo et al. 2019). Since humans have a finite attentional resource, distraction therapy for minimising pain associated with medical procedures is believed to be effective as it consumes a proportion of those resources and leaves less cognitive capacity available for processing pain (Chirico et al. 2016).

As a minimum, VR requires a display that allows the user to see the virtual environment. In the most common consumer systems this is achieved through a HMD that displays images on two screens in front of the user's eyes. In smartphone-based VR systems, the HMD consists of a smartphone wrapped in an inexpensive case with lenses and the phone provides both the computing power and display. In more powerful systems, the content displayed on the headset is generated by a desktop or laptop computer (Won et al. 2017). Higher-tech VR systems (high display quality, head tracking, headphones, sound effects and user interactivity) may be more effective at reducing pain than low-tech VR systems (Li et al. 2011, Indovina et al. 2018). A non-exhaustive list of VR consumer systems can be found in Table 1 – adapted from Won et al. (2017). Immersive VR interventions can be also achieved through multi-modal VR platforms that offer an alternative to real environments or via VR glasses.

There are uncertainties regarding the need for CE marking as medical devices for the VR systems used for distraction therapy in order to minimise pain associated with medical procedures. The VR systems used in the RCTs of this report used commercially available VR systems and did not account for the regulatory status of anu content displayed as part of the intervention.

Table 1. A non-exhaustive list of VR HMD systems - adapted from Won et al. (2017)

Head and hand tracking, computer or other systems linked VR systems		
Product name	**System specifications**	**Appropriate age for use**
HTC Vive (4 variations)	HMD and hand trackers – whole room VR with positional and rotational tracking	Minimum 7+ (depending on app)
Oculus Rift (2 variations)	HMD and hand trackers – with positional and rotational tracker	13+
HP Reverb	HMD and hand trackers – with positional and rotational tracker	13+
PlayStation VR	Video game console HMD and hand trackers – with positional and rotational tracker	12+
Head and hand tracking, required smartphone for set-up		
Product name	**System specifications**	**Appropriate age for use**
Oculus Go	HMD and single hand tracker – with positional and rotational tracker	13+
Oculus Quest	HMD and single hand tracker – with positional and rotational tracker	13+
Head tracking, requires smartphone as display		
Product name	**System specifications**	**Appropriate age for use**
Google Cardboard	Requires VR-compatible smartphone, single use – with rotational tracking	Unspecified
Google Daydream	Requires VR-compatible smartphone – with rotational tracking and one controller	13+
Samsung Gear VR	Requires VR-compatible smartphone, includes controller – with rotational tracking	13+
Other systems		
Product name	**System specifications**	**Appropriate age for use**
Lenovo Mirage	Standalone system, requires internet connection, includes motion controller – positional tracking	14+
VR – virtual reality, HMD – head-mounted display		

4. Existing guidance

In April 2018, the ECRI Institute published a Health Technology Assessment Hotline Response on the use of "Immersive Virtual Reality for Relieving Pain and Anxiety in Pediatric Patients during Procedures." The health technology appraisal (HTA) was conducted based on evidence published between January 2008 and March 2018 of various designs, including systematic reviews, randomised controlled studies and quasi-experimental studies. They concluded that the evidence is somewhat favourable for the technology in question and that the limited evidence originating from controlled studies and systematic reviews suggests that immersive VR may reduce pain and anxiety more than standard of care in children and adolescents. The procedures covered in the review included venepuncture, wound dressing changes, physical therapy for burns and dental procedures. It was also acknowledged that more randomised controlled trials are needed to confirm the results and to establish the effectiveness of VR in different clinical settings.

To our knowledge, there are no existing evidence-based guidelines or guidance on the use of virtual reality that are relevant to UK clinical practice.

5. Evidence search methods

We searched for evidence that could be used to answer the review question: what is the clinical and cost effectiveness of virtual reality as a distraction therapy for the management of procedural pain? We included studies of people who have, or are at risk of, experiencing pain caused by medical procedures such as wound/burn dressing changes, dental procedures, IV access/venepuncture, childbirth, or cancer pain due to chemotherapy or other therapeutic procedures. We searched for studies that compared immersive VR as a method of pain management to standard of care: depending on the condition, this could include pharmaceutical analgesia, anaesthesia, alternative methods of distraction, or non-immersive virtual reality. We included studies irrespective of the content displayed in the VR intervention, method of delivery or the level of immersion achieved by the different VR systems. We extracted data from relevant studies on any pain-related outcomes (usually pain intensity), and also outcomes related to anxiety/distress, procedure completion outcomes such as time required and success rate, quality of life, resource use and adverse events.

The detailed criteria used to select evidence are detailed in Appendix 1. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts. The search for relevant literature was conducted, but not restricted to the following databases: Medline, Embase, PsycINFO, Cochrane Library, CRD and Epistemonikos. The concepts used were "virtual reality" AND "pain." The search was restricted only for articles in English. No date limit was applied to the search. The full search strategy is available on request.

Appendix 2 summarises the selection of articles for inclusion in the review.

6. Clinical effectiveness

The literature search identified a systematic review by Georgescu et al. (2019) entitled "Psychological interventions using virtual reality for pain associated with medical procedures: a systematic review and meta-analysis." This systematic review was identified as the most relevant to use in the context of this appraisal as their inclusion criteria closely matched the criteria we developed for this review. The study selection criteria included RCTs in patients of any age undergoing a painful procedure that compares an immersive VR-based intervention with treatment as usual and that reported any pain outcomes. Since pain was measured on different scales in the

included studies, standardised mean differences (SMD) were calculated by the authors in order to compute random-effects meta-analyses. Certain studies reported pain intensity measured both real-time and retrospectively. For the purposes of this appraisal, we extracted the real-time measurements of pain intensity where available and the retrospective measurements for those studies that did not measure the sensory component of pain in real-time. A total of 23 RCTs of both crossover and parallel designs were deemed suitable. The medical procedures covered in the selected studies included dental restorative treatment (two RCTs), dressing change for wounds, burns or injuries (12 RCTs), IV access (three RCTs), surgery (one RCT) and physical therapy for burns (five RCTs). Twelve RCTs were conducted on paediatric patients, eight on adults and three RCTs had mixed-age populations.

A second systematic review and meta-analysis by Eijlers et al. (2019b) evaluated the effects of VR interventions on pain and anxiety specifically in paediatric populations. Three additional studies were identified in the systematic review by Eijlers et al. (2019b) that were not included in Georgescu et al. (2019). The medical procedures covered in the studies included restorative dental treatment, dressing change for burns and lumbar puncture solely in paediatric patients.

Lastly, a systematic review and meta-analysis by Mallari et al. (2019) evaluated the efficacy of VR as an analgesic for acute and chronic pain in adults. We extracted an additional three RCTs not included in Georgescu et al. (2019) that focused on acute pain as a result of medical procedures. The studies investigated the efficacy of VR in minimising pain during labour, dressing change for wounds and burns, and during cystoscopy.

An additional 32 RCTs deemed suitable for this appraisal and not included in the reviews described above were found in our literature search. The medical procedures covered include dental procedure (nine RCTs), IV access (12 RCTs), colonoscopy (two RCTs), dressing change for haemorrhoidectomy (one RCT), dressing change for burns (one RCT), physical therapy for burns (one RCT), labour (one RCT), cystoscopy (one RCT), elective cephalic version (one RCT), peri-operative pain control, elective maxillofacial surgery (one RCT) and elective day care surgery (one RCT).

The characteristics of the studies included in the meta-analysis are summarised in Table 2. For each study we extracted the study design, target population, the intervention including the type of immersive VR used, the comparator including the type of analgesia used (where available), the medical procedure and the pain outcome measured with the corresponding scale. Given the sufficient number of RCTs identified, we did not include any other study designs in this appraisal.

Table 2. Study characteristics

Study reference	Design, Population	Intervention	Comparator	Medical Procedure	Pain Outcome (Scale)
Georgescu et al. (2019) – Systematic review					
Bentsen et al. (2001)	RCT, Crossover Paediatric – n=46	VR distraction (video glasses)	Treatment as usual (TAU) – no analgesic used	Restorative dental treatment	Pain intensity (Visual Analog Scale – VAS)
Brown et al. (2014)	RCT, Parallel Paediatric – n=99	VR distraction (multi modal design – MMD) and analgesia	TAU including analgesia (opioids)	Dressing change for burns	Pain intensity (FACES Pain Scale Revised – FPS-R)
Carrougher et al. (2009)	RCT, Crossover Adults – n=78	VR distraction (video glasses) and analgesia	TAU including analgesia (opioids)	Physical therapy for burns	Worst pain (VAS)
Chan et al. (2007)	RCT, Crossover Paediatric – n=16	VR distraction (head mounted display – HMD)	TAU including analgesia (opioids and NSAIDs)	Dressing change for burns	Pain intensity (FACES)
Frere et al. (2001)	RCT, Crossover Adults – n=50	VR distraction (video glasses)	TAU – no analgesic used	Restorative dental treatment	Pain intensity (Graphic Rating Scale – GRS)
Gerceker et al. (2018)	RCT, Crossover Paediatric – n=80	VR distraction (HMD)	TAU – no analgesic used	IV access (phlebotomy)	Pain intensity (FACES)
Gershon et al. (2004)	RCT, Parallel Paediatric – n=40	VR distraction (HMD) and analgesia	TAU including analgesia (local)	IV access (cancer treatment)	Pain intensity (VAS)
Gold&Mahrer (2018)	RCT, Parallel Paediatric – n=141	VR distraction (video glasses)	TAU – no analgesic used	IV access (phlebotomy)	Pain intensity (VAS)
Guo et al. (2015)	RCT, Parallel Adults – n=98	VR distraction (video glasses)	TAU – no analgesic used	Dressing change for injuries	Pain intensity (VAS)

Table 2. Continued

Study reference	Design, Population	Intervention	Comparator	Medical Procedure	Pain Outcome (Scale)
Hoffman et al. (2000)	RCT, Crossover Adults – n=24	VR distraction (video glasses) and analgesia	TAU including analgesia (opioids)	Physical therapy for burns	Average pain (VAS)
Hoffman et al. (2001)	RCT, Crossover Mixed – n=14	VR distraction (video glasses) and analgesia	TAU including analgesia (not reported)	Physical therapy for burns	Average pain (VAS)
Hoffman et al. (2008)	RCT, Crossover Mixed – n=22	VR distraction (HMD) and analgesia	TAU including analgesia (opioids)	Dressing change for burns	Worst pain (GRS)
Hua et al. (2015)	RCT, Parallel Paediatric – n=64	VR distraction (HMD)	Distraction only	Dressing change for wounds	Pain intensity (FACES)
JahaniShoorab et al. (2015)	RCT, Parallel Adults – n=30	VR distraction (video glasses) and analgesia	TAU including analgesia (local)	Surgery for episiotomy repair	Pain intensity (Negative Response to Pain – NRP)
Jeffs et al. (2014)	RCT, Parallel Paediatric – n=18	VR distraction (HMD) and analgesia	TAU including analgesia (opioids)	Dressing change for burns	Pain intensity (VAS)
Kipping et al. (2012)	RCT, Parallel Paediatric – n=41	VR distraction (HMD) and analgesia	TAU including analgesia (opioids and NSAIDs) and distraction	Dressing change for burns	Pain intensity (VAS)
Konstantatos et al. (2009)	RCT, Parallel Adults – n=86	VR distraction (video glasses) and analgesia	TAU including analgesia (opioids)	Dressing change for burns	Pain intensity (VAS)
Maani et al. (2011)	RCT, Crossover Adults – n=24	VR distraction (HMD) and analgesia	TAU including analgesia (opioids)	Dressing change for burns	Worst pain (GRS)
Miller et al. (2010)	RCT, Parallel Paediatric – n=40	VR distraction (MMD) and analgesia	TAU including analgesia (opioids) and distraction	Dressing change for burns	Pain intensity (FACES)

Table 2. Continued

Study reference	Design, Population	Intervention	Comparator	Medical Procedure	Pain Outcome (Scale)
Miller et al. (2011)	RCT, Parallel Paediatric – n=40	VR distraction (MMD) and analgesia	TAU including analgesia (opioids and NSAIDs) and distraction	Dressing change for burns	Pain intensity (FACES)
Morris et al. (2010)	RCT, Crossover Adults – n=22	VR distraction (HMD) and analgesia	TAU including analgesia (not reported)	Physical therapy for burns	Pain intensity (Numeric Pain Rating Scale (NPRS)
Schmitt et al. (2011)	RCT, Crossover Mixed – n=108	VR distraction (HMD) and analgesia	TAU including analgesia (opioids)	Physical therapy for burns	Worst pain (GRS)
van Twillert et al. (2007)	RCT, Parallel Paediatric – n=38	VR distraction (HMD)	TAU including analgesia (not reported) and distraction	Dressing change for burns	Pain intensity (VAS)
Eijlers et al. (2019b) – Systematic review (additional suitable studies not included in Georgescu et al. (2019))					
Asl Aminabadi et al. (2012)	RCT, Crossover Paediatric – n=120	VR distraction (video glasses) and analgesia	TAU including analgesia (not reported)	Restorative dental treatment	Pain intensity (FACES)
Das et al. (2005)	RCT, Crossover Paediatric – n=11	VR distraction (video glasses) and analgesia	TAU including analgesia (not reported)	Dressing change for burns	Pain intensity (FACES)
Sander Wint et al. (2002)	RCT, Parallel Paediatric – n=30	VR distraction (video glasses) and analgesia	TAU including analgesia (not reported)	Lumbar puncture	Pain intensity (VAS)
Mallari et al. (2019) – Systematic review (additional suitable studies not included in Georgescu et al. (2019))					
Frey et al. (2019)	RCT, Crossover Adults – n=27	VR distraction (HMD)	TAU – No VR	Labour	Pain during contractions (NPRS)

Table 2. Continued

Study reference	Design, Population	Intervention	Comparator	Medical Procedure	Pain Outcome (Scale)
McSherry et al. (2018)	RCT, Crossover Adults – n=18	VR distraction (HMD) and analgesia	TAU – including analgesia (opioids)	Dressing change for burns and wounds	Pain intensity (Verbal Numeric Scale – VNS)
Walker et al. (2014)	RCT, Parallel Adults – n=45	VR distraction (HMD) and analgesia	TAU – including analgesia (topical)	Cystoscopy	Average pain during procedure (VAS)
Additional studies identified					
Al-Halabi et al. (2018)	RCT, Parallel Paediatric – n=101	VR distraction (HMD) including oral anaesthesia	TAU – including oral anaesthesia and basic behaviour guidance or distraction with tablet/phone	Dental inferior alveolar nerve block	Pain intensity (FACES)
Alshatrat et al. (2019)	RCT, Within-subject Adults – n=50	VR distraction (HMD)	TAU – no VR	Dental periodontal scaling and root planning	Worst pain (VAS)
Atzori et al. (2018)	RCT, Crossover Paediatric – n=15	VR distraction (HMD)	TAU – no VR	IV access (venepuncture)	Worst pain (VAS)
Aydin&Ozyazicioglu (2019)	RCT, Parallel Paediatric – n=120	VR distraction (HMD)	TAU – no VR	IV access (venepuncture)	Pain intensity (VAS)
Chan et al. (2019)	2 RCTs, Parallel Paediatric – n1=123, n2=129	VR distraction (HMD) including analgesia	TAU – including analgesia (topical or systemic)	IV access in emergency department and outpatients	Pain intensity (Faces Pain Scale – FPS-R)
Chen et al. (2019)	RCT, Parallel Paediatric – n=136	VR distraction (HMD)	TAU – no VR	IV access (injections)	Pain intensity (Wong-Baker FACES Pain Rating Scale – WBFPS)
Ding et al. (2019)	RCT, Parallel Adults – n=182	VR distraction (HMD) in addition to TAU	TAU – including analgesia (NSAIDs)	Dressing change for haemorrhoidectomy	Pain intensity (VAS)

Table 2. Continued

Study reference	Design, Population	Intervention	Comparator	Medical Procedure	Pain Outcome (Scale)
Dunn et al. (2019)	RCT, Parallel Paediatric – n=24	VR distraction (HMD)	TAU – distraction, no VR	IV access for haemophilia treatment	Pain intensity (modified VAS/FACES)
Eijlers et al. (2019a)	RCT, Parallel Paediatric – n=191	VR distraction (HMD)	TAU – no VR	Elective maxillofacial, dental or Ear, Nose or Throat (ENT) surgery	Pain intensity (FPS-R)
Gold et al. (2006)	RCT, Parallel Paediatric – n=20	VR distraction (HMD) in addition to TAU	TAU - including local analgesia	IV access	Pain intensity (FPS-R)
Hoffman et al. (2019)	RCT, Parallel Paediatric – n=44	VR distraction (video glasses) in addition to TAU	TAU – including analgesia (not reported)	Dressing change for burns	Worst pain (GRS)
Koc Ozkan&Polat (2019)	RCT, Parallel, 3 arms Paediatric – n=135	VR distraction (video glasses)	No VR and other distraction method	IV access (venepuncture)	Pain intensity (VAS-WBFPS)
Niharika et al. (2018)	RCT, Crossover Paediatric – n=40	VR distraction (video glasses)	Crossover design – different phases of treatment had no VR distraction	Dental pulp therapy of primary molars	Pain intensity (WBFPS)
Nunna et al. (2019)	RCT, Parallel Paediatric – n=70	VR distraction (HMD) including analgesia	TAU – including analgesia (topical)	Dental injection for pulpectomy	Pain intensity (WBFPS)
Shetty et al. (2019)	RCT, Parallel Paediatric – n=120	VR distraction (video glasses) in addition to TAU	TAU – including analgesia (topical)	Dental pulpectomy	Pain intensity (WBFPS)
Soltani et al. (2018)	RCT, Parallel Adults – n=39	VR distraction (video glasses) in addition to TAU	TAU including analgesia (opioids) and benzodiazepines	Physical therapy for burns	Worst pain intensity (GRS)
Umezawa et al. (2015)	RCT, Parallel Adults – n=60	VR distraction (HMD) – silent movie	Wore VR headset but did not watch a movie	Colonoscopy	Pain intensity (VAS)

Table 2. Continued

Study reference	Design, Population	Intervention	Comparator	Medical Procedure	Pain Outcome (Scale)
Walther-Larsen et al. (2019)	RCT, Parallel Paediatric – n=64	VR distraction (HMD) and analgesia	TAU – including analgesia (topical)	IV access (cannulation)	Pain intensity (VAS)
weta et al. (2019)	RCT, Parallel Adults – n=50	VR distraction (HMD)	TAU – No VR	Dental anaesthesia administration	Pain intensity (VAS)

RCT – randomised controlled trial, VR – virtual reality, TAU – treatment as usual, VAS – visual analogue scale, FPS-R – FACES pain scale revised, MMD – multi-modal design, NSAID – nonsteroidal anti-inflammatory drugs, GRS – graphic rating scale, IV – intravenous, NRP – negative response to pain, NPRS – numeric pain rating scale, VNS – verbal numeric scale, WBFPS - Wong-Baker FACES pain rating scale

6.1. Pain intensity outcomes

SMD and 95% confidence intervals were extracted from the relevant systematic reviews. For the additional studies identified, effects sizes were computed as SMD in Stata v.16 using the number of participants randomly allocated to each intervention, the mean pain score and the corresponding standard deviation and further transformed in the adjusted Hedges' g. Where multiple values for pain intensity were reported by the authors for multiple timepoints, the pain score that was the closest associated with the time of the intervention was extracted. We pooled pain score outcomes from a total of 40 studies and calculated an overall effect using random effects meta-analysis. A summary of the pain intensity outcome data included in the meta-analysis can be found in Table 2. Cohen's guidelines were used to interpret the magnitude of the SMD, where an SMD of 0.2 shows a small effect, 0.5 an intermediate effect and 0.8 is suggestive of a large effect. For 13 RCTs the SMDs could not be pooled due to insufficient reporting of data by the authors. The outcomes of these studies were reported separately in Table 4.

Table 3. Outcome data for pain intensity included in the meta-analysis

Study reference	Outcome (SMD with 95% Confidence Interval)	Population (n)
Asl Aminabadi et al. (2012)	1.85 (1.42 - 2.28)	120
Atzori et al. (2018)	0.68 (-0.06 - 1.42)	15
Aydin and Ozyazicioglu (2019)	0.05 (-0.3 - 0.41)	120
Bentsen et al. (2001)	0.17 (-0.15 - 0.49)	46
Brown et al. (2004)	0.3 (-0.09 - 0.69)	99
Carrougherer al. (2009)	0.48 (0.16 - 0.81)	78
Chan et al, (2007)	0.5 (-0.17 - 1.16)	16
Chan et al. (2019) - ED	0.42 (0.07 - 0.78)	123
Chan et al. (2019) - OPD	0.37 (0.02 - 0.72)	129
Chen et al. (2019)	0.37 (0.03 - 0.71)	136
Das et al. (2005)	1.16 (0.25 - 2.06)	11
Ding et al. (2019)	0.17 (-0.12 - 0.46)	182
Frere et al. (2001)	1.28 (0.76 - 1.8)	50
Gerceker et al. (2018)	1.77 (1.26 - 2.28)	80
Gershon et al. (2004)	0.51 (-0.15 - 1.16)	40
Gold and Mahrer 2018	0.35 (0.02 - 0.68)	141
Gold et al. (2006)	0.27 (-0.61 - 1.15)	20
Guo et al. (2014)	1.93 (1.45 - 2.41)	98
Hoffman et al. (2000)	1.09 (0.4 - 1.77)	24

Table 3. Continued

Study reference	Outcome (SMD with 95% Confidence Interval)	Population (n)
Hoffman et al. (2001)	1.21 (0.2 - 2.22)	14
Hoffman et al. (2008)	0.81 (0.17 - 1.46)	22
Hoffman et al. (2019)	1.28 (0.66 - 1.91)	44
Hua et al. (2015)	0.88 (0.38 - 1.38)	64
JahaniShoorab et al. (2015)	0.99 (0.24 - 1.73)	30
Jeffs et al. (2014)	0.46 (-0.43 - 1.36)	18
Kipping et al. (2012)	0.14 (-0.46 - 0.74)	41
Koc Ozkan and Polat (2019)	2.73 (2.15 - 3.32)	135
Konstantatos et al. (2009)	0.57 (0.14 - 1)	86
Maani et al. (2011)	0.6 (0.02 - 1.18)	24
McSherry et al. (2018)	0.41 (0.09 - 0.74)	18
Miller et al. (2010)	2.26 (1.39 - 3.12)	40
Miller et al. (2011)	2.57 (1.74 - 3.4)	40
Morris et al. (2010)	0.46 (-0.12 - 1.04)	22
Niharika et al. (2018)	1.35 (0.61 - 2.08)	40
Nunna et al. (2019)	-0.03 (-0.49 - 0.44)	70
Sander Wint et al. (2002)	0.3 (-0.42 - 1.03)	30
Schmitt et al. (2011)	0.52 (0.27 - 0.77)	108
Soltani et al. (2018)	0.4 (-0.24 - 1.04)	39
van Twillert et al. (2007)	0.5 (0.04 - 0.96)	38
Weta et al. (2019)	0.46 (-0.1 - 1.02)	50
SMD – standardised mean difference		

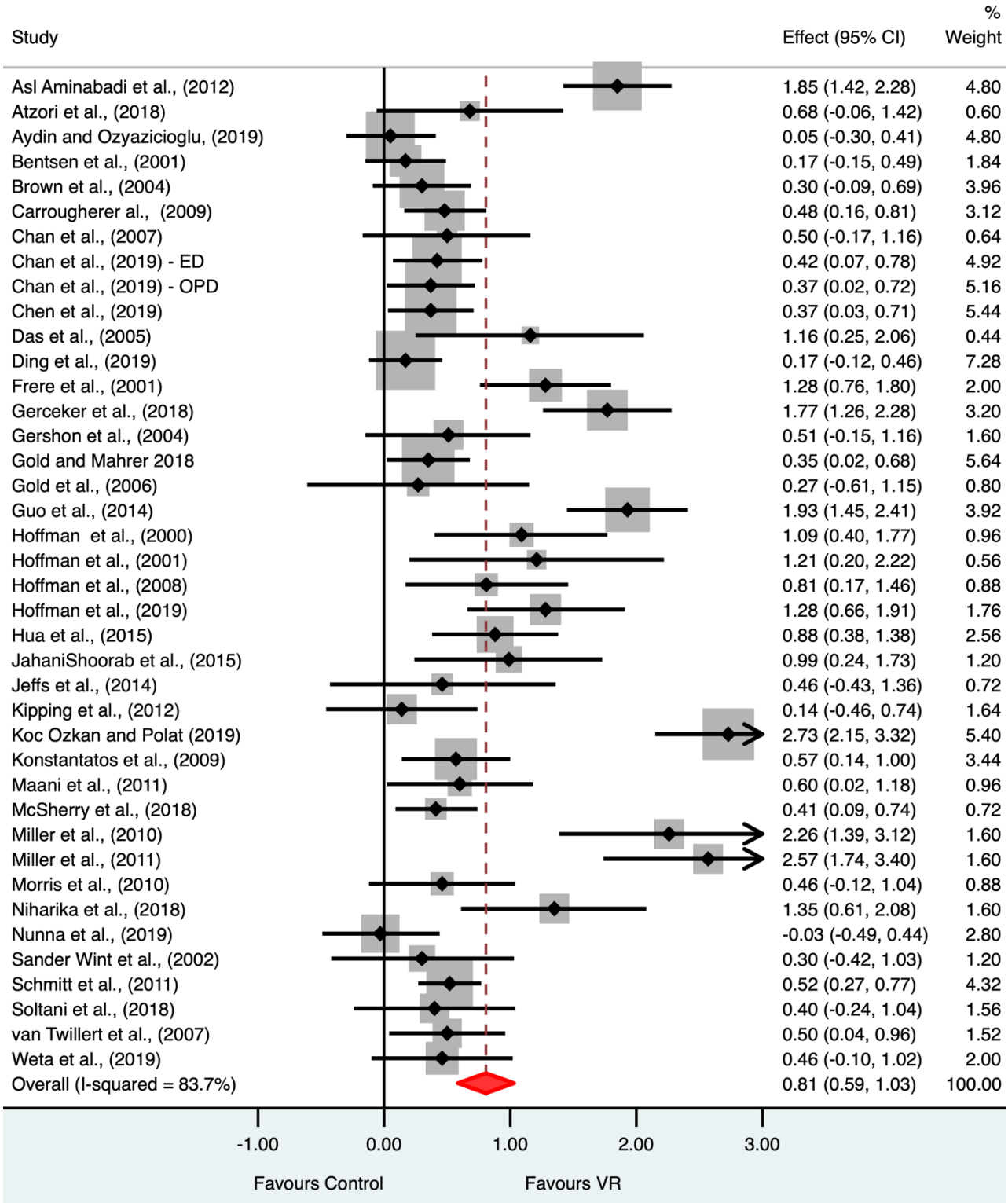

Figure 1. Forest plot of standardised mean difference for pain intensity outcomes for VR-based interventions in comparison to treatment as usual (control).

A total number of 40 RCTs covering a population of 2501 patients (adult and paediatric) were included in the meta-analysis for assessing the effectiveness of VR on pain-related outcomes during medical procedures (Figure 1). Across all studies the weighted effect size of VR interventions on minimising medical procedural pain was large with an indicative SMD=0.81, 95% CI 0.59 to 1.03, p=0.000 and tau^2=0.2926. This indicates a substantial clinical benefit; however there is a high amount of detected heterogeneity with I^2=83.7%. We further performed a meta-regression accounting for the population age investigated in the included studies (adult versus paediatric patients). In the meta-regression and further sub-group analysis we excluded the three studies by Hoffman et al. (2001), Hoffman et al. (2008) and Schmitt et al. (2011) which included mixed populations in their investigations. The meta-regression did not show a statistically significant difference in the effect between the two populations (regression coefficient of -0.09, 95% CI -0.59 to 0.41, p=0.720 tau^2=0.4151). We further computed sub-group analysis for the two populations in order to observe the difference in the effect between the two groups (Figure 2). The analysis for the adult population included 12 RCTs with a representative population of 701 patients. Similarly the analysis for the paediatric population included 25 RCTs covering a population of 1656 patients. Across all the studies in the paediatric sub-group analysis the effect of VR intervention at minimising pain outcomes remained high, with SMD=0.86, 95% CI 0.54 to 1.19, p=0.000 and I^2=87.1%. Conversely, the analysis for the adult population shown an intermediate to large effect with a SMD=0.71, 95% CI 0.36 to 1.06, p=0.000 and I^2=78.1%. Nevertheless, as aforementioned, the difference in the effect between the two populations is not statistically significant as indicated in the meta-regression.

Consequently, we investigated if there is any variation in effectiveness of VR interventions in minimising pain outcomes in relation to the different medical procedures. Since no statistically significant difference was observed in the effect between adult and paediatric patients both populations were included in the stratification by medical procedures. The studies that included mixed population were included in this analysis. The emergent categories for the sub-group analysis by medical procedures were the following: dental treatment, dressing change for burns and wounds, IV access and physical therapy for burns. The study by Ding et al. (2019) which investigated the effect of VR interventions for the treatment following haemorrhoidectomy, as well as the studies by JahaniShoorab et al. (2015) and Sander Wint et al. (2002) which looked at the effects of VR post-surgery for episiotomy repair and respectively lumbar puncture were excluded from the sub-group analysis.. We further computed a meta-regression and sub-group analysis by medical procedure. The meta-regression did not show a statistically significant difference in the effect of the VR intervention between the investigated medical procedures (regression coefficient of -0.08, 95% CI -0.33 to 0.17, p=0.509 tau^2=0.3961) – Figure 3. The analysis for the dental treatment procedure included six RCTs with a representative population of 376 patients while the dressing change for burns and wounds group included 15 RCTs covering a population of 659 patients. The IV access group included ten RCTs from a patient population of 939 patients and lastly the physical therapy for burns group covered six RCTs with a population of 285 patients. Across all the sub-groups, the greatest effect of the VR intervention was observed in people having dressing changes for burns and wounds with SMD=1.01, 95% CI 0.63 to 1.39, p=0.000 and I^2=80.9. The dental treatment sub-group showed a large effect across all the studies with SMD=0.98, 95% CI 0.28 to 1.68, p=0.006 and I^2=91.1%. Similarly, the IV access subgroup shows a large effect as a result of the VR intervention with SMD=0.80, 95% CI 0.32 to 1.28, p=0.001 and I^2=89.7%. Lastly, the physical therapy for burns sub-group shows an intermediate effect with SMD=0.57, 95% CI 0.39 to 0.75, p=0.000 and I^2=0.0%. It is notable that regardless of the medical procedure the VR intervention shows a positive effect on pain outcomes; however, the difference in the effect between procedures is not statistically significant as indicated by the meta-regression. Treatment effect for dental treatment showed the highest degree of heterogeneity while the equivalent result for physical therapy for burns had an associated I^2 of 0%.

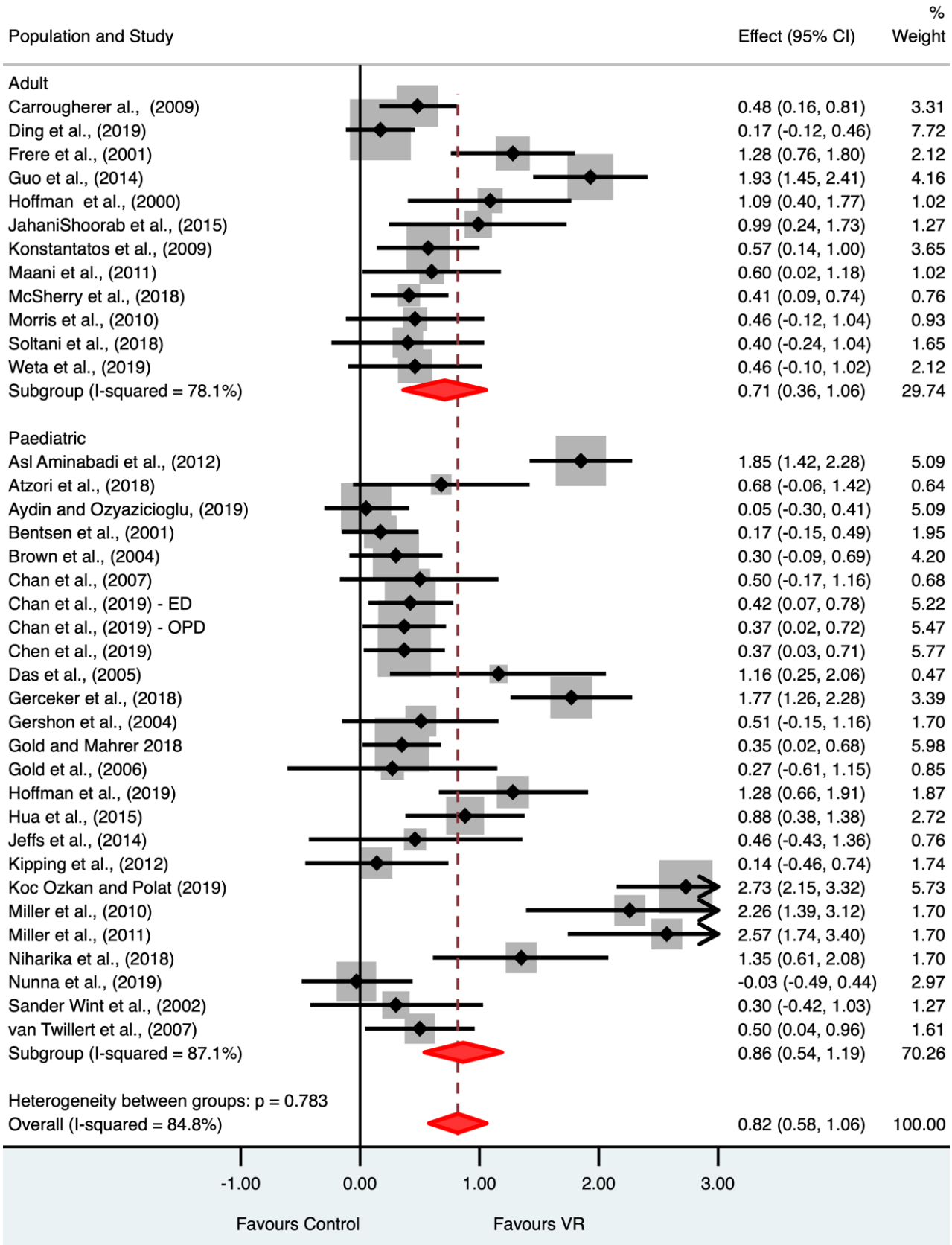

Figure 2. Forest plot of standardised mean difference for pain intensity outcomes by age group for VR-based interventions in comparison to treatment as usual (control).

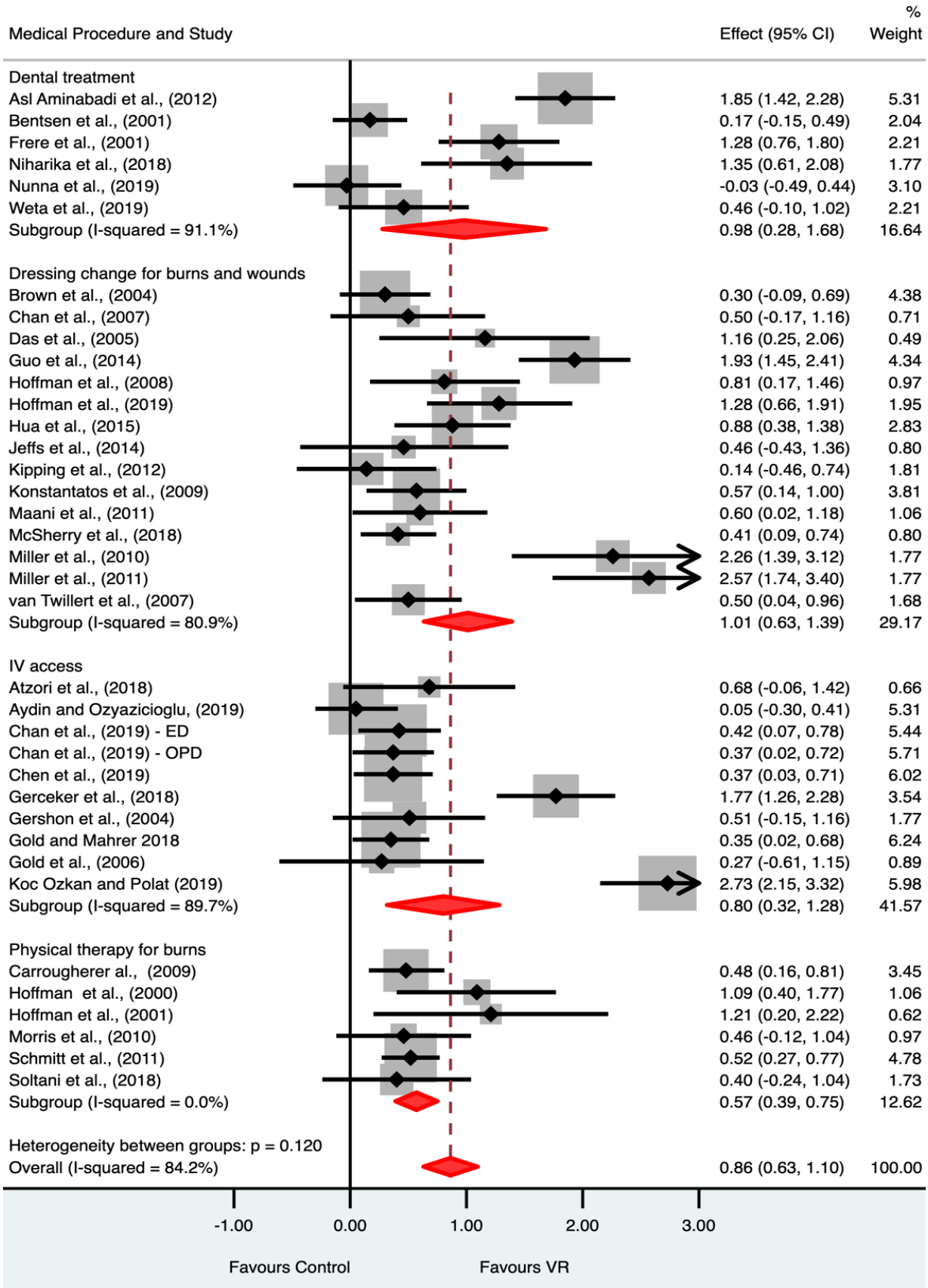

Figure 3. Forest plot of SMD for pain intensity outcomes by medical procedure for VR-based interventions in comparison to treatment as usual (control).

Table 4. Outcome data for pain intensity from studies not included in the meta-analysis

Study reference	Pain outcome reported	Population (n)
Al-Halabi et al. (2018)	No statistically significant difference in the W-B FACES scores as a result of the intervention (p=0.536)	101
Alshatrat et al. (2019)	Average pain perception (VAS) significantly lower in the VR group (mean rank 11.05) compared to no VR (mean rank 10.00) with Z=-4.030, p=0.000, r=0.4	50
Caruso et al. (2020)	No difference in the change of procedural pain scores (increased, unchanged or decreased) measured on FPS-R scale with p=0.62	220
Dunn et al. (2019)	No statistically significant difference between VR and TAU for the pain intensity (VAS/FACES), median=3 (pre- and post-intervention) on a scale from 0-100	24
Eijlers et al. (2019a)	No statistically significant differences were found between VR and TAU (FPS-R) post-procedure with p=0.699 (recovery room) and p=0.454 (home)	191
Frey et al. (2019)	Worst pain intensity (NPRS) was significantly lower in the VR group with the slope estimate -1.5 (95% CI, -0.8 to -2.2)	27
Haisley et al. (2020)	No statistically significant differences in pain scores (0-10 scale) in the first day post-op – VR group mean 3.8 and non-VR group 3.9 with p-0.88 - or in the worst pain in the first 24 hours (0-10 scale) – VR group mean 6.3 and non-VR group 6.6 with p=0.49.	52
Ozalp Gerceker et al. (2019)	A statistically significant difference was found between groups according to the self-, parent-, researcher- and nurse-reported pain scores (W-B FACES) with p<0.05	136
Shetty et al. (2019)	General trend of lower pain scores on WB-FACES between the two groups as a result of the VR intervention (p<0.001)	120
Smith et al. (2020)	No statistically significant differences were observed in the pain scores as a result of the intervention – VR 60.68±21.1 vs control 49.76±28 with p=0.17	50
Umezawa et al. (2015)	No statistically significant differences between the two groups in regard to the pain experienced during the procedure, with median=24.5, IQR 33.25 (range 0-96) for VR and median=42, IQR 52 (range 0-100), p=0.47	60

Table 4. Continued

Study reference	Pain outcome reported	Population (n)
Walker et al. (2014)	Similar average pain during procedure in both groups with VR average pain of 44 mm and control 43 mm	43
Walther-Larsen et al. (2019)	No statistically significant difference in the pain intensity (VAS) between the VR group (median=27, IQR 8 to 33) and control (median=15, IQR 5 to 30), p=0.23	64
W-B FACES – Wong-Baker FACES, VR – virtual reality, FPS-R – FACES pain scale revised, NPRS – numeric pain rating scale, IQR – interquartile range		

As can be observed in Table 4, four of the RCTs covering a population of 333 patients showed a positive effect of VR interventions on minimising pain associated with medical procedures. Unfortunately, due to insufficient reporting standards of the data, those studies could not be included in the meta-analyses. The residual nine RCTs that covered a population of 805 patients failed to demonstrate a positive effect for VR interventions in medical procedures. The three studies that showed a positive effect of VR interventions on pain outcomes covered medical procedures such as labour, IV placement and dental treatment that are already included in our pooled analysis. The nine studies that failed to demonstrate a positive effect of VR interventions covered the following medical procedures: dental inferior alveolar nerve block, IV access for haemophilia treatment or cannulation, elective maxillofacial, dental or ENT surgery, colonoscopy, external cephalic version, peri-operative pain control and cystoscopy. Those medical procedures and associated conditions were not covered in our meta-analysis or any of the sub-group analyses. Therefore, given the nature of the medical procedure it is reasonable to conclude that those results would not affect the validity of the conclusions derived from the meta-analysis.

6.2. Other procedural/pain outcomes

The systematic review by Georgescu et al. (2019) reported the affective and cognitive components of pain as their secondary outcome. The absolute benefits were reported as numbers-needed-to-treat (NNT) in order to generate one additional positive outcome. The affective components of pain were aggregated from the time spent thinking about pain and worry. Conversely, the cognitive components of pain were aggregated from pain unpleasantness, anxiety and distress. Accordingly, they identified five studies that assessed the affective component of pain real-time (g=0.94 (95% CI 0.33 to 1.56), NTT=2.02, I^2=51% (95%, 0 to 94)) and 14 studies retrospectively (g=0.55 (95% CI 0.34 to 0.77), NTT=3.30, I^2=58% (95%, 4 to 86)). The cognitive component was assessed only retrospectively in eight studies, (g=0.82 (95% CI 0.39 to 1.26), NTT=2.28, I^2=75% (95%, 24 to 95))

The second systematic review by Eijlers et al. (2019b) that focused solely on paediatric populations, computed a meta-analysis on the effect sizes for patient reported anxiety from seven studies. They report a large effect size for VR interventions on anxiety (SMD=1.32, 95% CI 0.21 to 2.44, I^2=96.6%, p=0.020). Given the high heterogeneity, a sensitivity analysis was performed by excluding one of the outlying studies. The analysis still showed a positive effect of VR on anxiety (SMD=0.50, 95% CI 0.20 to 0.79, I^2=22.4, p=0.001).

Additional systematic reviews identified in our literature search were scrutinised in order to identify additional outcomes measured as part of VR interventions for medical procedural pain. A systematic review and meta-analysis of RCTs for procedural pain management of burn patients during dressing change and physical therapy by Luo et al. (2019) was identified. They computed meta-analyses for outcomes other than pain intensity. All the studies included in their meta-analyses were already identified and included in the meta-analysis of pain outcomes. Their additional outcomes included measures of unpleasantness, time spent thinking about pain, and fun. Significantly less unpleasantness was experienced as a result of the VR intervention in comparison to the control group – seven studies (MD=2.06, 95% CI 1.23 to 2.89, I^2=77%, p<0.0001). In the same seven studies patients were found to spend less time thinking about pain in the VR group than control (MD=3.31, 95% CI 2.15 to 4.46, I^2=86%, p<0.00001). Four studies reported the level of fun experienced by the patients during the trial. More fun was experienced by the patients as a result of the VR intervention (MD=-5.50, 95% CI -5.57 to -5.43, I^2=78%, p<0.00001). In addition to the meta-analyses of secondary outcomes, the systematic review reports presence and realism from nine trials. The average scores ranged from 3.51 to 6.367 out of 10. One study reported that a presence greater than 3.4 is associated with a better pain reduction.

In a systematic review by Won et al. (2017) on "Immersive Virtual Reality for Paediatric Pain" additional outcomes were reported from two of the studies already included in our meta-analysis. The RCT by Brown et al. (2004) showed not only a decrease in self-reported pain and anxiety in paediatric patients undergoing dressing changes but also an increased rate of epithelialisation and faster wound healing in the VR intervention group (-2.14 days, 95% CI -4.38 to 0.1, p=0.061). This was significantly faster when adjusted for mean burn depth (-2.26 days, 95% CI -4.48 to -0.04, p=0.046). The second study by Miller et al. (2010) showed that that when a multimodal intervention was utilised, the procedure required less time to complete (p<0.05).

Lastly, a systematic review by Indovina et al. (2018) reports studies that assessed VR usability and impact on treatment duration in order to evaluate the feasibility in a clinical setting. Although no significant differences were found in terms of treatment duration, interviews with nurses dealing with the children with burns revealed that VR interventions can calm children and thus increase their co-operation, making medical procedures less challenging and time-consuming. Conversely, another study reported that implementing VR in a burn centre suggested that the setup, patient training, treatment and equipment cleaning require a significant amount of staff time and commitment which can represent a hurdle for the use of VR in clinical practice.

6.3. Adverse events

The systematic review by Georgescu et al. (2019) included 12 studies that evaluated adverse effects of the VR intervention. In one study 15% of the participants reported nausea and in a second study 5.2% reported nausea and 8% simulator sickness. In the rest of the trials, none or under 5% of the participants reported nausea.

In the systematic review by Luo et al. (2019), 11 trials reported incidence of nausea as none, negligible or mild with no other side effects reported. Similarly, the systematic review by Indovina et al. (2018) on use of VR as a distraction for pain and distress during medical procedures, reports that nausea or other possible side effects of the VR intervention were evaluated in most studies. The authors state that nausea was very infrequent and mild and no other side effects were reported. They also highlight that in almost all of the studies nausea occurrence was only measured for VR treatment alongside analgesia without performing a comparison to the control condition. Therefore, the authors suggest that the few cases of nausea cannot be entirely attributed to the VR intervention because nausea could also be due to the use of opioid analgesics.

Experts consulted during this appraisal highlighted that research should be conducted regarding the long-term effects of VR use on posture or eyesight. We did not identify any sources of evidence that addressed this issue.

6.4. Risk of publication bias

The risk of publication bias for the studies included in our meta-analysis of the effectiveness of VR intervention to minimise pain associated with medical procedures was assessed by generating funnel plots. The funnel plot (Figure 4A) shows asymmetry indicating the presence of publication bias where a greater effect size of the intervention is shown by studies conducted on smaller populations. The contour-enhanced funnel plot also suggests that most studies show statistical significance at a conventional threshold of $p<0.05$. The presence of publication bias could explain some of high heterogeneity between the studies included in the meta-analysis. Egger's regression asymmetry tests did confirm the presence of significant publication bias (intercept 3.15, 95% CI 1.09 to 5.22, $p=0.004$).

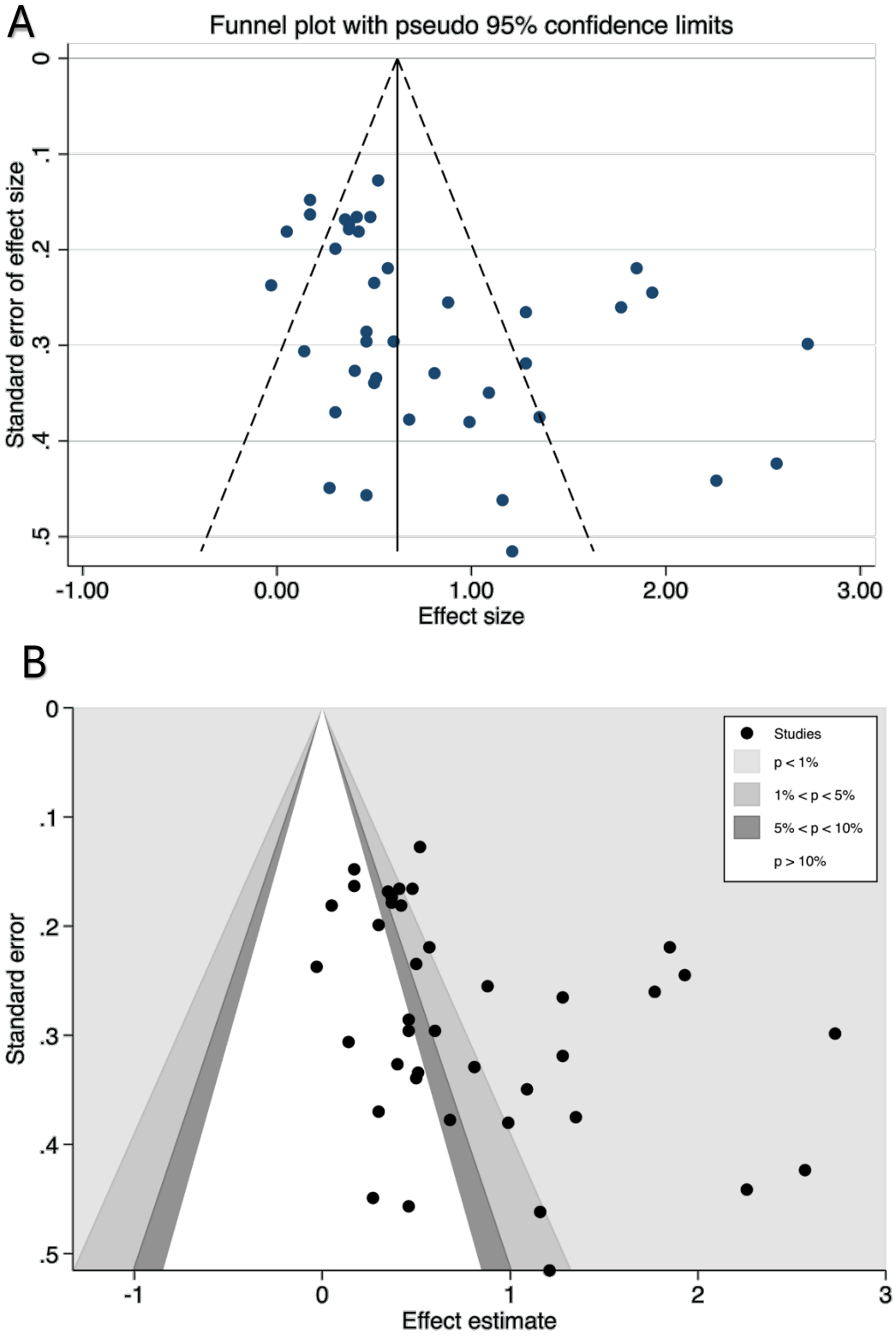

Figure 4. A-Funnel plot, B-Contour-enhanced funnel plot for the meta-analysis assessing the effects of VR interventions in minimising pain associated with medical procedures (n=40 RCTs)

6.5. Sensitivity analysis

Georgescu et al. (2019) addressed the uncertainties regarding the high levels of observed heterogeneity and large effect sizes that favour VR interventions by sensitivity analysis. Publication bias was also addressed with the Henmi-Copas estimate. Accordingly, they performed a series of sensitivity analyses on the total 23 RCTs they included in their analysis. A decreased effect size was noticed with the exclusion of four potential studies classified as outliers (g=0.66, 95% CI 0.46 to 0.85, I^2=53%, 95% CI for I^2 8 to 81); exclusion of three studies that had multi-modal interventions (g=0.77, 95% CI 0.51 to 1.02, I^2=78%, 95% CI for I^2 60 to 90); exclusion of four trials that did not have an intervention control (g=0.77, 95% CI 0.41 to 1.14, I^2=87%, 95% CI for I^2 68 to 95). Smaller effects were also noticed across the 11 crossover trials (g=0.61, 95% CI 0.34 to 0.88, I^2=57%, 95% CI for I^2 1 to 89). Higher effect sizes were observed: when the analysis was restricted to dressing change for burns (11 studies, g=1.03, 95% CI 0.37 to 1.68, I^2=91%, 95% CI for I^2 78 to 97) and in studies with a parallel design (11 studies, g=1.08, 95% CI 0.46 to 1.70, I^2=92%, 95% CI for I^2 82 to 98). Similar effects were observed when the analysis was restricted to the paediatric population (11 studies, g=0.87, 95% CI 0.17 to 1.57, I^2=94%, 95% CI for I^2 85 to 98) or in trials that randomised a minimum of 20 participants per arm (14 studies, g=0.97, 95% CI 0.44 to 1.51, I^2=94%, 95% CI for I^2 87 to 98). Their observations regarding the restriction of the analysis on dressing change for burns and wounds or paediatric populations are consistent with our findings from the computed meta-regressions and sub-group analyses. The authors also addressed if there is any difference in the effect size resulting from the use of analgesia. Accordingly the difference between the studies that used concomitant analgesia (16 studies, g=0.78, 95% CI 0.37 to 1.19) in comparison to those that did not (6 studies, g=1.09, 95% CI 0.33 to 1.86) was not significant (p=0.36). Lastly, publication bias addressed with the Henmi-Copas estimate shows similar effect sizes for both real-time (9 studies, g=0.77, 95% CI 0.22 to 1.33, I^2=79%, 95% CI for I^2 65 to 96) and retrospective study designs (22 studies, g=0.69, 95% CI 0.36 to 1.01, I^2=82%, 95% CI for I^2 80 to 95).

While some heterogeneity could be explained in the sensitivity analyses conducted by Georgescu et al. (2019), it is clear that VR interventions still show benefit in minimising pain associated with medical procedures. Although publication bias was identified and the Egger's regression confirmed statistically significant small study effects, the Henmi-Copas estimate still favours VR interventions over TAU. Furthermore, the use of concomitant analgesia does not seem to affect the effect size of the intervention at a statistically significant threshold.

6.6. Clinical interpretation of pain outcomes

In order to provide a clinical interpretation and translation of the findings, the SMD of the studies that measured pain on VAS from Georgescu et al. (2019) were converted to mean differences. This was achieved by calculating an average standard deviation from the individual standard errors and number of patients included in each study. The SMD were further multiplied by the average standard deviation in order to convert the results into mean differences expressed on VAS. A total number of 14 studies included in the systematic review measured pain on VAS for the VR intervention. Accordingly, after conversion the results ranged from 0.27 to 5.09 with an average of 1.85 reduction in pain on VAS as a result of the VR intervention. Experts advise that a clinically relevant reduction in pain could be reflected by a reduction in drugs used to manage pain or that is repeatable and similar to a painkiller. A 30% reduction on a 10- or 11-point numeric rating scale of pain appears to be the consensus of the measurement of a clinically relevant reduction.

6.7. Ongoing trials

We also searched for ongoing randomised controlled trials of VR, compared to any control treatment, as a method of procedural pain management. Because of the large number of

potentially relevant trials identified (n = 351), we only included trials that planned to recruit at least 100 participants, and had a planned or actual completion date no later than February 2021.

We identified 21 eligible trials, the design and characteristics of which are summarised in Appendix 3. The procedures studied included IV access (five RCTs), fracture treatment (two RCTs) and mixed procedures (five RCTs); a single RCT was identified studying each of hysteroscopy, spinal injection, scar treatment, orthopaedic procedures, labour, bone biopsy, wound sutures, cystoscopy and immunisation. Twelve trials recruited paediatric patients whilst the remaining nine recruited adults.

7. Economic evaluation

7.1. Economic evidence review

No economic evidence was identified on the use of VR distraction therapy in the specific population considered in this guidance (people at risk of pain cause by medical procedures). Some economic evidence was identified on the use of VR distraction therapy in other patient groups. Most notably, an exploratory analysis by Delshad et al. (2018) considered the use of VR distraction therapy for pain in hospitalised patients. The analysis was exploratory and aimed to identify cost and effectiveness thresholds that VR therapy would need to meet to be cost saving. The analysis showed the potential for VR to be cost saving if it resulted in reductions in opioid utilization and hospital length of stay.

7.2. Estimated cost of VR

The table below gives estimated costs for some of the most commonly used commercially available VR systems (note that the list of VR systems is non-exhaustive). Costs were estimated by taking an average price from various retail stores where the product was available (prices accurate as of 5th February 2020).

In addition to the commercially available VR systems, there are bespoke VR packages available, which have been specifically designed for use in healthcare. These bespoke packages are available for an annual licence fee. Delshad et al. (2018) reported a VR annual license cost of $3,500 (£2,512) for the package offered by AppliedVR.

Rescape also offer a VR system for use in healthcare (DR.VR) and provided further details of what is included within such a package. In addition to the VR headset, the package includes an accompanying tablet and software which allows the clinician to view and control the VR experience of the patient without the need to use hospital Wi-Fi as it has an independent Wi-Fi connection. The software includes functionality for patient data capture using questionnaires and data storage using an online portal. The system also includes a solution for infection control using hygiene facemasks. Upgrades to hardware and software as well as free replacements for breakages are also included as part of the annual license fee.

Table 5. Estimated costs of commercially available VR systems

Product name	Estimated cost	Source
Head and hand tracking, computer or other systems linked VR systems		
HTC Vive Cosmos	£699	Average of prices from Currys and Amazon
HTC Vive Pro starter kit	£1,119	Average of prices from Currys and Amazon
Oculus Rift (2 variations)	£397	Average of prices from Currys, Amazon and John Lewis
HP Reverb	£559	Price from Amazon
PlayStation VR	£243	Average of prices from Currys and Amazon
Head and hand tracking, required smartphone for set-up		
Oculus Go 32GB	£139	Average of prices from Currys, Amazon and John Lewis
Oculus Go 64GB	£189	Average of prices from Currys, Amazon and John Lewis
Oculus Quest 64GB	£399	Average of prices from Currys and John Lewis
Oculus Quest 128GB	£499	Average of prices from Currys and John Lewis
Head tracking, requires smartphone as display		
Google Cardboard	£15	Price from Google store
Google Daydream	£75	Average of prices from Carphone Warehouse and BT Shop
Samsung Gear VR	£116	Average of prices from Amazon and BT Shop
Other systems		
Lenovo Mirage	£400	Average of prices from Amazon and BT Shop

In addition to the equipment and software costs, there would also be staff costs associated with operating the VR system. Delshad et al. (2018) reported a salary cost of $47,030 (£33,755) for a "virtualist" technician who would be responsible for optimizing VR therapeutic delivery to patients. However, where VR systems are currently in use in the NHS Wales, they are being delivered by existing staff members. The time required for staff members to use the VR system are not known but a systematic review by Indovina et al. (2018) suggests that setup, training, treatment and cleaning require a significant amount of time and may be a hurdle for the use of VR in clinical practice.

8. Organisational issues

As aforementioned, a study that investigated the implementation of VR interventions in a burn centre suggested that the setup, patient training, treatment and equipment cleaning require a significant amount of staff time and commitment which can represent a hurdle for the use of VR in clinical practice (Indovina et al. 2018). Staff training for the use of VR as a distraction therapy

may also be required for the correct implementation of such interventions. Experts advise that potential barriers associated with the implementation of VR interventions in clinical practice could be reflected by the time required to set up the systems, explanation of interventions to the patients, decontamination, IT support and staff training.

In addition to training, adherence to infection control standards could be challenging to implement with VR technologies. One potential way to mitigate against this issue would be the use of disposable and inexpensive cardboard VR systems. However, it is unclear whether these systems are as effective in pain management as higher-tech VR systems (analysis of this is beyond the scope of this report). Alternative infection control solutions could include disinfection procedures that do not damage the VR systems, or replacement of components that are in contact with the patients' skin during the use of the system. Experts advise that UV sterilisation of the VR systems, disinfection of the hard-plastic surface with standard fungicidal surface wipes as well as the use of disposable paper face masks that minimise the contact of the systems with the patients' skin could be a viable solutions to mitigate against potential infection control issues.

With regard to regulatory issues, we did not identify any VR systems that are CE marked as medical devices. Although the use of VR systems in healthcare has rapidly gained popularity, based on the evidence identified it appears that medical professionals use commercially available systems (i.e. the ones detailed in Table 1) that are not explicitly covered by medical device regulations in their interventions. Therefore, it remains unclear what are the regulatory issues for VR systems in healthcare interventions and what standards these devices need to adhere to.

9. Patient issues

We did not identify any evidence that reported on patients' experiences of using, or their perception of using VR as a method of procedural pain management. HTW conducted a two-pronged search for patients in Wales using VR devices to manage their experiences of pain during medical procedures by conducting a patient organisation search for charities and patient networks as well as via the clinical experts identified through the clinical evidence. We looked for patient groups/organisations associated with the medical conditions that were identified in the clinical evidence including burns/wounds, pregnancy and labour, children's health, cancer and restorative dentistry. Of the fifteen patient organisations contacted, no patients currently using VR to manage pain during medical procedures were found. Several organisations reported their intention to look into the use of VR in the future. Out of the four areas where clinicians reported that they are currently using VR in Wales, only the Cystic Fibrosis Unit based in University Hospital Llandough provided a report regarding the multiple uses of VR for patients suffering from cystic fibrosis generated from research they had previously conducted. One of the outcomes measured in the context of their investigation was the reduction in pain and anxiety experienced by patients while using the VR. The Cystic Fibrosis Unit advised that their on-going research into VR was stopped until they figured out a solution to mitigate against the associated infection control issues. However, the unit had ten patients who were currently able to use their VR devices and they agreed to work with HTW to produce a questionnaire for each patient to complete. This questionnaire was produced and disseminated to patients; however, no completed questionnaires were returned.

Therefore, the key considerations from a patient and public involvement perspective on the use of VR for the management of acute pain associated with medical procedures remain the following:

- There is evidence that VR can be used in a variety of ways across a wide range of patient groups and health conditions and that it is an emerging technology for the management of the pain experienced by patients during medical procedures in Wales.
- Uptake of this technology in Wales appears to be selective to specific, singular units and does not appear to be widespread across Health Boards, patient groups or health conditions. Furthermore, it does not appear to be any consistency in the way in which VR devices are being used or obtained by clinicians or patient organisations.
- Most of the organisations, clinicians and researchers that responded to HTW's requests appear to be considering the use of VR as a future intervention for their patients and have expressed interest in more information and guidance concerning its use.
- It is unclear how many patients in Wales have had the opportunity to use VR to manage their pain during medical procedures, but from the responses received from the clinicians it would appear that the numbers are few.
- There is evidence from research conducted by the Cystic Fibrosis Unit in University Hospital Llandough that VR is successful in reducing the experience of anxiety and associated pain in patients with cystic fibrosis.
- Research continues to advance in the use of VR for a variety of interventions across patient groups and health conditions. Initial reports of patient experience do appear to support the evidence that VR is effective and suggests that it is a valuable option for some patients.

10. Conclusions

Based on pooled analysis of randomised controlled trials, immersive VR interventions appear to be effective at reducing pain intensity associated with medical procedures compared with treatment as usual. Both adult and paediatric populations appear to benefit of such interventions with the observed effect sizes being large in paediatric populations and intermediate to large in adults. With regard to the medical procedures, VR interventions show large effect sizes in dressing change for wounds and burns, dental treatment and IV access and an intermediate effect in physical therapies for burns. Despite the high heterogeneity identified and the risk of publication bias, previously conducted sensitivity analyses strengthen the validity of the conclusion. This evidence appraisal report included RCTs irrespective of the device delivery system, level of immersion achieved by the different devices or the content displayed during the medical procedure. Experts advise that further research needs to be conducted in order to define the right level of immersion and content to be displayed in order to maximise the positive effects of VR interventions in clinical practice.

Although VR interventions appear to be effective in minimising pain associated with medical procedures, a number of organisational issues were identified that could hinder the implementation of VR interventions in clinical practice. Firstly, no VR delivery systems that are CE marked as medical devices were identified. Additionally, more rigorous and uniform approaches should be defined in order to mitigate against the infection control issues associated with the use of the devices in patient populations. Despite these barriers, experts advise that VR interventions could be very relevant in a clinical context as they provide a 'do no harm', low cost adjunct that could minimise the psychological and physiological aspects of both interventional and diagnostic procedures. They also note that any non-pharmacological option for pain reduction is worth exploring since the healthcare is experiencing an opioid crisis and that it could also be relevant in palliative and day surgery care as well as for the management of chronic pain.

11. Contributors

This topic was proposed by Dr Jamie Duckers, Consultant Physician, Cardiff and Vale University Health Board, and Matthew Wordley, CEO, Rescape Innovation.

The HTW staff and contract researchers involved in writing this report were:

- A Mironas – clinical lead and primary author
- D Jarrom – co-author and project design
- J Washington – literature searches
- A Evans – patient and public involvement co-ordinator and co-author
- M Prettyjohns – co-author and health economics
- H Britton – project management

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

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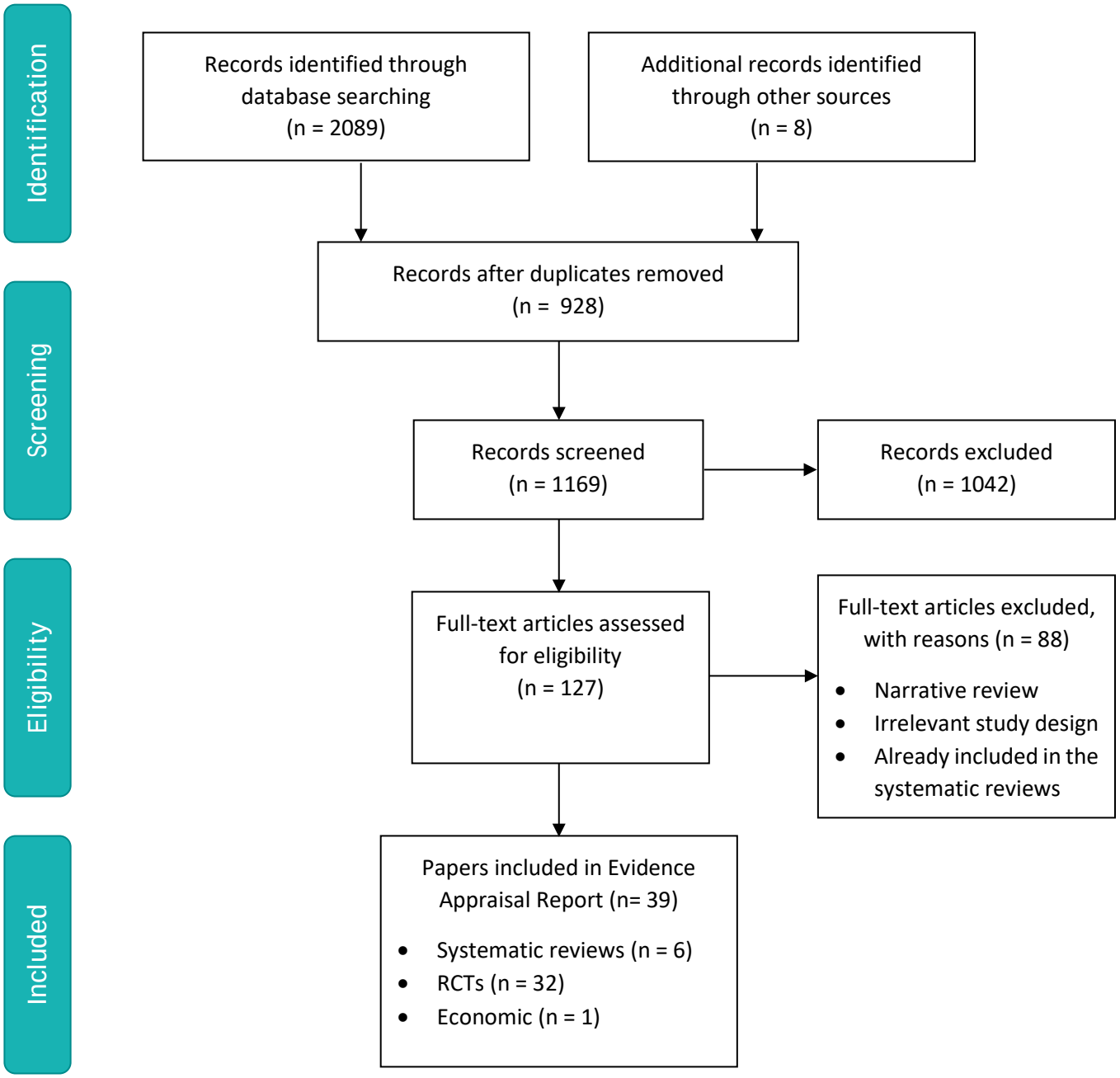
Appendix 1. Selection criteria to studies included in the review

Research Question	What is the clinical and cost effectiveness of virtual reality as a distraction therapy for the management of procedural pain?

	Inclusion criteria	**Exclusion criteria**
Population	People who have or are at risk of procedural pain, caused by procedures such as, but not limited to: • Dressing changes for wounds or burns • Dental procedures • Cancer pain due to chemotherapy or other procedures • IV access/venepuncture • Routine outpatient procedures • Labour	
Intervention	Immersive (interactive or non-interactive) virtual reality as a distraction therapy (delivered by a head-mounted display, with or without sound) The intervention will usually be an adjunct or addition to standard care, but may also be a replacement for standard care in some circumstances: either scenario will be considered	Virtual reality as an exposure therapy Non-immersive virtual reality
Comparison/ Comparators	Standard care The comparator will vary according to the condition, symptom or procedure alongside which virtual reality is used. Examples include, but are not limited to: • Alternative methods of distraction • Non-immersive virtual reality • Analgesia • Anaesthesia	
Outcome measures	Pain-related outcomes: • General pain levels • Changes in severity/intensity of pain • Changes in pain threshold/tolerance • Duration of pain (reduction) • Changes in pain distribution • Pain frequency • Time spent thinking about pain • Strongest pain intensity Other procedure related outcomes: • Behavioural distress/distress symptoms • Perceived treatment time • Procedure-related anxiety	

	• Perceived unpleasantness • Psychological arousal • Time to complete procedure • Rate of successfully completed procedures Changes in other disease-specific outcomes: • Changes in quality of life • Rates of hospital admission/changes to care delivery • Length of stay • Post-procedural care • Changes in healthcare resource use Adverse events: • As a result of intervention • As a result of procedure
Study design	We will include the following clinical evidence in order of priority: • Systematic reviews. • Randomised trials. • Non-randomised trials. We will only include evidence for "lower priority" evidence where outcomes for each condition/symptom of interest are not reported by a "higher priority" source. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison.
Search limits	No date limits. English language articles only.
Other factors	If there is sufficient evidence we will carry out subgroup analysis on the effectiveness of VR in: • Different age groups (eg adults, paediatrics) • Different clinical applications and settings

Appendix 2 - PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness (no date restriction, evidence searched up until March 2020)



Appendix 3. Characteristics of the identified ongoing trials

Study title/ID	Design, Population	Intervention	Comparator	Outcomes	Completion date
NCT04081935, Distraction Using VR for Children During IV in an Emergency Department	Population: children (aged 7 to 12 years) receiving intravenous injections at an emergency department. Setting: Taiwan Enrolment: 136 (actual)	VR distraction therapy	TAU	Pain intensity Fear	May 2018 (actual)
NCT03888690, Effect of Virtual Reality Distraction on Procedural Pain for Children and Adolescents in Onco-Hematology Unit. (ReVaDo)	Population: children (aged 8 to 17 years) with onco-haematological pathologies undergoing any invasive procedures Setting: France Enrolment: 96 (estimated)	VR in combination with TAU	TAU	Pain Anxiety	June 2020 (estimated)
NCT03827824, Virtual Reality on Perception of Pain and Anxiety by Hysteroscopy (Hysteroscopy)	Population: Women (aged 18 to 75 years) with an established indication for diagnostic hysteroscopy Setting: Spain Enrolment: 176 (estimated)	VR in combination with TAU	TAU	Pain Anxiety Blood pressure Cardiac frequency Oxygen saturation	January 2020 (estimated)
NCT03641859, Evaluation of Pain and Anxiety in Patients With an Invasive Procedure in Emergencies (URGENCES_RV)	Population: adults undergoing invasive procedures (wounds or male patients requiring an urinary catheter) Setting : France Enrolment: 300 (estimated)	VR plus local anaesthesia	Local anaesthesia	Pain Anxiety Patient satisfaction	October 2020 (estimated)
NCT03787147, Assessing the Efficacy of Virtual Reality Analgesia (VRA) in Adult Patients for Pain Control During Spinal Injections (SI) (VR adult)	Population: adults receiving spinal injections Setting: USA Enrolment: 108 (estimated)	VR plus analgesia	Analgesia	Pain Anxiety Heart rate Blood pressure Body temperature	December 2020 (estimated)

Study title/ID	Design, Population	Intervention	Comparator	Outcomes	Completion date
NCT03784352, Virtual Reality Pediatric Orthopaedic Outpatient Procedures (VPRO)	Population: children (aged 4 to 12 years) undergoing orthopaedic outpatient procedures (cast application, cast removal, hardware removal, suture and staple removal, botox injections) Setting : Canada Enrolment: 240 (estimated)	VR plus TAU	TAU	Pain Anxiety Procedure time Nausea	November 2019 (estimated)
NCT03740607, Virtual Reality for Alleviation of Peripheral IV Placement-Associated Discomfort	Population: adults (aged 19 89 years) undergoing peripheral intravenous catheter placement Setting : USA Enrolment: 100 (estimated)	VR plus TAU	TAU	Discomfort Pain Adverse events Patient satisfaction Physiological parameters	March 2020 (estimated)
NCT03495531, Virtual Reality in Obstetric Patients	Population: obstetrics patients undergoing various child-labouring procedures Setting: USA Enrolment: 230 (estimated)	VR plus TAU	TAU	Anxiety Pain Patient satisfaction Epidural dosing requirements	May 2020 (estimated)
NCT03483194, Therapeutic Virtual Reality : Impact on the Management of Pain and Anxiety Related to Hematology Care (REVEH)	Population: adults (18 years and over) with malignant haematological pathology who must have an osteo-medullary biopsy for diagnostic purposes Setting: France, multicentre Enrolment: 126 (estimated)	VR plus local anaesthesia	Local anaesthesia	Pain Tolerance of procedure Anxiety Patient satisfaction Staff satisfaction Drug consumption due to procedure	June 2020 (estimated)

Study title/ID	Design, Population	Intervention	Comparator	Outcomes	Completion date
ACTRN12618001363279, Virtual Reality for Immunisation Pain: A Randomised Controlled Clinical Trial in General Practice	Population: children (4 years of age) receiving routine immunisations Setting: Australia Enrolment: 100 (planned)	VR	Other distraction techniques	Pain	February 2020 (estimated)
NCT03645213: Two Different Distraction Methods on Pain and Fear During Venipuncture in Children	Population: children (aged 7 to 12 years) who required a blood sample to be taken Setting: Turkey Enrolment: 120 (actual)	VR	Other distraction techniques, or TAU	Pain Fear	August 2018 (actual)
NCT03352752, Virtual Reality Technology to Alleviate the Acute Pain of Scar Treatment With Fractional Laser Under Local Anesthesia	Population: adults (aged 18 to 60 years) undergoing scar treatment with fractional laser Setting: China Enrolment: 218 (estimated)	VR	TAU	Pain Anxiety Physiological parameters Operating time Procedure success rate	December 2020 (estimated)
ACTRN12617000285358, Investigating the Management of paediatric procedural Pain Relief Obtained through Virtual Reality (IMPROVR)	Population: children required to undergo needle-based procedures Setting: Australia Enrolment: 240 (planned)	VR	TAU	Pain Ease of performing the procedure Procedure time Anxiety Patient satisfaction	February 2018 (actual)
NCT04040036, Effects of Virtual Reality on Pain, Fear and Anxiety During Blood Draw in Children Aged 5-12 Years Old	Population: children (aged 5 to 12 years) who underwent blood draw procedure Setting: Turkey Enrolment: 136 (actual)	VR	TAU	Pain Fear Anxiety	December 2017

Study title/ID	Design, Population	Intervention	Comparator	Outcomes	Completion date
DRKS00020229, Distraction of stress and pain in children by applications from virtual reality using the example of K-wire removal	Population: children (6 to 15 years old) after distal humerus or distal radius/forearm fracture with surgical treatment using K-wire osteosynthesis Setting: Germany Enrolment: 144 (planned)	VR	TAU	Heart rate Heart rate variability Blood pressure FLACC Pain Scale mYPA Scale Questionnaire	Expected duration 1.5 years
IRCT20151003024317N7, Evaluation of the effect of virtual reality on pain reduction in emergency department patients during suture	Population: adults undergoing suture of open wounds of unspecified body region Setting: Iran Enrolment: 120 (planned)	VR	TAU	Pain relief Patient satisfaction	March 2020
RBR-6J2XS9, Virtual reality during urological procedures	Population: adults attending urology services for elective cystoscopy Setting: Brazil Enrolment: 150 (planne	VR	TAU	Pain perception Difficulty of the procedure	Not mentioned
NCT04081935, Distraction Using VR for Children During IV in an Emergency Department	Population: children (7 to 12 years old) required intravenous injections at an emergency department Setting: Taiwan Enrolment: 136 (actual)	VR	TAU	Experienced pain Experienced fear	May 2018
NCT04152447, Virtual Reality for Pain Management in Orthopaedic Patients	Population: adults who suffered sustained fractures treated with open reduction internal fixation Setting: USA Enrolment: 200 (planned)	VR	TAU	Opioid usage Length of stay Pain scores	January 2021

NCT04268914, VR to Reduce Pre-Operative Anxiety	Population: children (10 to 21 years old) undergoing various procedures in the ambulatory surgery centre Setting: USA Enrolment: 450 (planned)	VR	TAU	Anticipatory anxiety measure Anxiety Pain Satisfaction Time of stay Malaise scale Blood pressure Heart rate Presence	October 2020
NCT04268901, VR to Reduce Pain/Anxiety During Painful Procedures	Population: children (10 to 21 years old) undergoing painful medical procedures Setting: USA Enrolment: 700 (planned)	VR	TAU	Anxiety Pain Facial affective scale Malaise Presence Satisfaction	December 2020
VR – virtual reality, IV – intravenous, TAU – treatment as usual, SI – spinal injections, FLACC – face, legs, activity, cry, consolability					