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Health-Related Quality of Life for Individuals with Hepatitis C: A Narrative Review

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Abstract

Background: The assessment of health-related quality of life (HRQoL) in hepatitis C (HCV) infected individuals continues to gain importance. However, rarely do reviews of this literature consider quantitative and qualitative accounts of HRQoL collectively, which only allows partial insight into the topic. This narrative review aims to address this gap in the literature. *Methods:* Literature searches were conducted using seven databases with two separate search strategies, and results assessed for eligibility using specific inclusion/exclusion criteria; a data extraction sheet was used to identify the dominant themes for each research paradigm which were then distilled to key findings to construct the narrative. *Results:* Quantitative investigation reveals a low HRQoL in individuals with HCV due to a complex multifactorial cause. During treatment for HCV, a further transient reduction is observed, followed by improvement if a sustained virological response is achieved. Qualitative data provide a recognisable voice to the everyday challenges experienced by individuals with HCV including insights into diagnosis and stigmatisation, contextualising how a reduced HRQoL is experienced day-to-day. Methodological limitations of these findings are then discussed. Much of the quantitative data has little relevance to current substance users as they are excluded from most trials, and appraisal of the qualitative literature reveals a marked difference in the lived experience of HCV infected current substance users and that of other HCV groups. *Conclusion:* Concurrent analysis of quantitative and qualitative paradigms provides a deeper understanding of the true burden of HCV illness on HRQoL. Greater utilisation of qualitative research within international clinical guidelines is likely to be of benefit in identifying relevant HRQoL outcomes for substance users.

Background

The latest reports estimate that worldwide between 130-150 million people are chronically infected with the hepatitis C virus (HCV), of which a significant number will go on to develop cirrhosis and hepatocellular carcinoma if left untreated (World Health Organisation, 2014). Within the UK, the most recent national estimates suggest around 214,000 individuals are infected (Public Health England, 2014), with injecting drug use continuing to be the most common route of viral transmission (Palmateer *et al*, 2013). In recent years, dramatic advances have occurred in drug therapy for HCV with the arrival of Direct Acting Antivirals, a group of drugs which directly inhibit viral reproduction and have significantly improved treatment success rates (Conteduca *et al*, 2014). Despite this, treatment uptake remains low, with UK estimates of approximately only 3-5% of those infected accessing antiviral therapy (Public Health England, 2014).

With the historical move from a disease-centred model of medicine to a more biopsychosocial paradigm, a focus has emerged on not only the biomedical decrements of illness and curative benefits of treatment, but also the experience of illness and treatment from the patient perspective (Fayers & Machin, 2007); commonly termed 'patient-reported outcome measures (PROMs)'. Increasingly, this focus is being given central importance in the planning of future healthcare improvements (e.g. Scottish Government, 2010) and the licencing of new medications (Food & Drug Administration, 2009), however PROMs are also used to inform clinical practice, aiding interaction and communication with patients and clients on a one-to-one basis (Wu & Snyder, 2012). Within the HCV research literature, the most commonly used quantitative PROM is Health-Related Quality of Life (HRQoL), a loosely defined term used to distinguish between aspects of life affected by disease or treatment for disease, and those broader quality of life issues such as access to green space within towns and cities (Fayers & Machin, 2007). HRQoL is ordinarily measured by standardised psychometric questionnaires, most commonly the 36-item Short Form Health

Survey (SF-36) (Ware & Sherbourne, 1992), however there is no consensus on this survey's exclusive use within HCV research, and numerous other tools also appear within the literature. 'Patient-reported outcome measures' is an umbrella term used to encompass any report coming directly from a patient about their health condition or treatment however, and in this vein there is also a body of qualitative research which provides a more in-depth focus on HRQoL, by examining particular aspects of the lived experience (Miller *et al*, 2012). Arguably, these two bodies of research complement each other, with qualitative studies giving a recognisable voice to the decrements and improvements in HRQoL described in the quantitative work; however by their use of different methods and focus on different populations they may also generate distinct insights into different HRQoL perspectives.

Existing reviews of the evidence in this area tend to focus on either qualitative or quantitative research and thus provide partial insight into the topic (e.g. Foster, 2009; Treloar & Rhodes, 2009). Miller *et al* (2012) did conduct a dual quantitative and qualitative systematic review of research published between 2000–2009, however did not compare the relative strengths and weaknesses of the findings produced by each paradigm and excluded interventional studies which contribute a large part of the quantitative literature in this area. The current review has been conducted to examine and synthesise the breadth of current research into HRQoL for people living with hepatitis C from both research paradigms.

Methods

The search strategy focused on seven databases; Medline, CINAHL, Embase, Cochrane Library, JBI COnNECT+, PsycINFO and ASSIA. Two separate search strategies were developed to identify both quantitative and qualitative reports. For quantitative papers, comparable search terms for 'Hepatitis C', 'Health-Related Quality of Life' (including common abbreviated forms) and 'Patient Reported Outcomes' were used, accounting for variation in the Subject Index Terms specific to each search engine. For qualitative papers, comparable search terms for 'Hepatitis C', 'Quality of Life' or 'Life Experience' and

'Qualitative Research' or 'Interview' were used, again accounting for variation in specific Subject Index Terms (the term 'quality of life' being used more generally within the qualitative literature than the more specific HRQoL). In order to obtain papers that provided a detailed historical and contextual view as well as giving contemporary relevance, databases were searched to the extent of their temporal limits, preceding the publication announcing the isolation of HCV (Choo *et al*, 1989) in most cases. Table 1 provides an example of the electronic search strategy conducted. The search was not limited to only those papers which focused on HRQoL in HCV positive injecting drug users, as we sought to examine the comparative differences in HRQoL between this group and other HCV infected individuals, in addition to contrasting the way each research paradigm reveals this. As the description of participants in studies varies (e.g. current injecting drug users, substance users, active injecting drug users, previous injecting drug users), often with little clarification of what these terms indicate, limiting the review by description of drug use status could also become specious and subjective. The generic term 'substance user' has been used within this review, except where injecting drug use is made explicit within the literature.

Inclusion and Exclusion Criteria

Figure 1 displays the results for the quantitative search strategy. The initial inclusion/exclusion criteria used were as follows: inclusion criteria were adult participants, an English language abstract, and specific quantitative HCV HRQoL data provided. Excluded papers were those dealing solely with other liver disease aetiologies, no HRQoL-related data, and papers concentrating on those undergoing haemodialysis or liver transplant, as these articles focused primarily on the impact of those specific interventions which is not the emphasis of this review. Both observational and interventional studies were included, as were reviews at this initial stage. Duplicate entries for the same article appearing in multiple search engines were removed. One hundred and fifty one articles and 18 reviews were then recovered, including seven articles identified from reference lists. Once examination of the reference lists was complete, review articles were then excluded as primary data sources.

The remaining retrieved articles were studied during which a further 30 papers were excluded for reasons shown in figure 1. All the remaining 121 papers have informed this review and the main findings from this body of work are presented here. Some of these references have not been further cited within the main text however for reasons of succinctness and economy. Full details of the 121 papers can be found in supplementary file 1.

Figure 2 demonstrates results for the qualitative search strategy. The inclusion criteria were as follows: adult participants, an English language abstract, 'life experience' focus and qualitative data reported. Exclusion criteria remained the same as the quantitative search strategy, and duplicate entries for the same article appearing in multiple search engines were removed. Seventy three articles were then recovered, including five reviews and eleven articles identified from reference lists. Review articles were then excluded as primary data sources. The retrieved articles were studied during which eleven further exclusions were made for the reasons identified in figure 2. All the remaining 57 papers have informed this review and the main themes from this body of work are presented here. However, not all articles have been further cited within the main text, and full details are given of all references in supplementary file 2. Records of all articles reviewed (n=178) were stored and managed online using RefWorks for both search streams.

Analysis

Data was extracted from each study by the lead author using a data extraction sheet which identified the author(s), date and source of publication, study design, key findings, limitations and recommendations, and inclusion of substance users. Using these data key dominant themes were identified for each research paradigm, which provided the foundation for the formulation of results and the synthesis of a coherent narrative. A narrative approach was adopted because of the variation in study design. A narrative review summarises different primary studies into a comprehensive holistic overview of the topic, rather than addressing

specific questions. Whilst narrative reviews are most commonly qualitative in nature, one of their strengths lies in drawing together the diverse understandings of a scholarly research topic (Jones, 2004) and therefore the approach fits this dual paradigm review well. The main themes identified in the literature for each paradigm will be explored in a chronological manner, with causal investigation and HRQoL before, during and after HCV therapy focused on from the quantitative literature first, followed by examination of qualitative research concentrating on the experience of diagnosis through to the experience of HCV therapy.

Results

Causal Investigation: Virus-Related Factors

The quantitative literature demonstrates HCV positive individuals have reduced HRQoL in comparison to healthy controls or population norms (Table 2) and goes onto investigate and debate the underlying cause for this. Foster, Goldin and Thomas (1998) reported reduced HRQoL in patients with HCV which could not be attributed to either the degree of liver disease, or association with a history of injecting drug use, concluding the decrement was attributable to HCV *per se*. Bonkovsky *et al* (1999) subsequently reported data from a large multi-centre drug trial which supported this hypothesis, concluding that HCV infection reduces HRQoL independent of comorbidities or factors associated with the virus. These studies spearheaded research in this area, and results from more recent observational studies give weight to the argument that viral-factors contribute to HRQoL independent of host-factors (John-Baptiste *et al*, 2009; Strauss *et al*, 2014). Whilst the mechanism for this is still debated, evidence of viral replication within the central nervous system adds weight to the argument (Forton *et al*, 2004).

It is unlikely that any one factor is solely responsible for reduced HRQoL however, and a complex multifactorial cause is a more likely explanation. Virus-related factors and associated extra-hepatic manifestations of HCV (such as cognitive impairment, fatigue and depression) compounded by host-related factors, psychiatric and medical co-morbidities and

the effects of stigma, are all likely to be significant contributors (Häuser *et al*, 2004; Helbling *et al*, 2008; Hsu *et al*, 2012). These will now be examined.

Causal Investigation: Host-Related Factors

The role of illicit substance use in relation to HRQoL decrements is an important consideration, given the high incidence of current or former substance users within this patient population (Hutchinson *et al*, 2006). Substance users experience a lower HRQoL than population norms irrespective of their HCV status (Dalgard *et al*, 2004; Gjeruldsen, Loge & Opjordsmoen, 2006; Fischer *et al*, 2013; McDonald *et al*, 2013), and former substance users who acquired the infection through injecting drug use have been shown to have lower HRQoL than individuals who acquired HCV by another route (Foster, Goldin & Thomas, 1998; Hollander, Foster & Weiland, 2006). Interestingly, a study by Dalgard *et al* (2004) reported that active injecting drug users (IDUs) who *believed* they were infected with HCV had poorer HRQoL than those who did not or who did not know their status, irrespective of their actual serostatus, implying the knowledge (or assumed knowledge) of HCV positive status impacts HRQoL in addition to actually being infected with the virus. This echoes earlier work from a much smaller sample which found people who injected drugs, but were unaware of their HCV positive status had better HRQoL than those who were aware of their infection 26 years after being infected (Rodger *et al*, 1999). A recent much larger study from Scotland supports these findings. McDonald *et al* (2013) assessed almost 3000 current IDUs accessing Injecting Equipment Provision Services in Scotland using the EQ-5D questionnaire and anonymised dried bloodspot testing, reporting a reduction in HRQoL between those who were aware of their HCV positive status and those who were not. Additionally, no difference in HRQoL was found between HCV negative IDUs and those who were HCV positive but unaware of their infection, supporting other work suggesting the impact of an undiagnosed HCV infection upon groups with already lower HRQoL than population norms places little additional burden, possibly due to the extent of co-morbidities present and overall lower HRQoL anyway (e.g. Schwarzingler *et al*, 2004; Thein *et al*, 2006).

In exploring the reasons for these findings however, it becomes evident that the quantitative data available fails to provide sufficient insight. Why does undiagnosed HCV fail to impact on HRQoL for this population when it has been demonstrated to have a detrimental effect in other groups such as blood donors? (E.g. Strauss *et al*, 2014). Is the negative 'label' of HCV constructed around preconceptions about the chronic nature of the virus and its historically poor treatment outlook, or from external influences such as societal stigma? These points will be returned to in due course, when the qualitative literature surrounding the lived experience of HCV is examined.

In addition to substance use, other comorbid psychiatric and medical problems have also been implicated in reducing HRQoL in HCV patients (Taliani *et al*, 2007; Hsu *et al*, 2012). Häuser *et al* (2004) argued that comorbidity is the best predictor of overall HRQoL reduction in patients with HCV, and further studies also highlight the importance of underlying medical and psychiatric comorbidities in reductions to both the mental health domains (Lim *et al*, 2006; Snow *et al*, 2010) and the physical domains (Kwan *et al*, 2008) of HRQoL assessment.

Causal Investigation: Stigma

As already described, substance users who were aware of their infection had lower HRQoL than those who were unaware (Rodger *et al*, 1999; McDonald *et al*, 2013) which may be due in part to the effects of stigmatisation towards these individuals which negatively affect their social status and self-image (Rodger *et al*, 1999). In one of the very few studies to combine a qualitative approach with a quantitative HRQoL assessment, Miller, Hiller and Shaw (2001) described patients' distress by the perceived stigma associated with HCV, however without this qualitative adjunct the effect of stigma is poorly understood in the majority of HRQoL quantitative research.

HRQoL Pre-Treatment

The impairment in HRQoL for individuals with HCV has been shown to be equivalent to, or more severe than, the impact on physical and general health experienced by patients with other chronic conditions such as hypertension, type II diabetes, arthritis or depression (Bayliss *et al*, 1998; Bonkovsky *et al*, 1999; Kallman *et al*, 2007) and has more impact on physical domains than hepatitis B in mono-infection (Foster, Goldin & Thomas, 1998; Bondini *et al*, 2007) and in HIV co-infected individuals (Gillis *et al*, 2013). Of note, HCV also has a negative impact on mental health, an area in which detriments in other conditions are generally smaller (Foster, 2009; Tillmann *et al*, 2011).

A reduction in HRQoL can occur even in the absence of cirrhosis or significant liver disease (Foster, Goldin & Thomas, 1998; Bonkovsky *et al*, 1999; Córdoba *et al*, 2003; Häuser *et al*, 2004; Rowan *et al*, 2005; Helbling *et al*, 2008), and does not appear to be associated with Alanine Aminotransferase (ALT) levels (Foster, Goldin & Thomas, 1998; Miller, Hiller & Shaw, 2001; Arora *et al*, 2006; von Wagner *et al*, 2006; Helbling *et al*, 2008). Where advanced significant liver disease does occur however, further reductions in HRQoL are reported on a sliding continuum from advanced bridging fibrosis, to compensated cirrhosis to decompensation (Córdoba *et al*, 2003; Bonkovsky *et al*, 2007; Kallman *et al*, 2007; Björnsson *et al*, 2009; Snow *et al*, 2010). Although most HRQoL domains are affected, reductions in physical components are most frequently noted as being most sensitive to the negative impact of cirrhosis (Bayliss *et al*, 1998; Córdoba *et al*, 2003; Bonkovsky *et al*, 2007; Kallman *et al*, 2007; Mandorfer *et al*, 2014). This low HRQoL in untreated HCV patients has been reported to have substantial economic costs to society, through loss of productivity, increased absenteeism from work and increased use of healthcare resources (El Khoury, Vietri & Prajapati, 2012; Liu *et al*, 2012).

HRQoL During-Treatment

The treatment of HCV has long been associated with a further transient reduction in HRQoL, largely attributed to the drugs used during therapy. For example, patients treated with

Interferon- α (IFN) with or without ribavirin (RBV) demonstrated a significant increase in depression (Hunt *et al*, 1997), severe treatment-related distress (Bianchi *et al*, 2000) and a general decline in HRQoL during the period of therapy, which then returned to or surpassed baseline levels by 24 weeks post-treatment for those patients who achieved a Sustained Virological Response (SVR) (Ware *et al*, 1999; McHutchison *et al*, 2001). With the pegylation of interferon (PEG-IFN) a reduced impairment in HRQoL and less fatigue were reported during PEG-IFN and RBV therapy compared to IFN & RBV, especially in the initial 12-24 weeks, which had important implications for reducing treatment discontinuation (Bernstein *et al*, 2002; Rasenack *et al*, 2003, Hassanein *et al*, 2004, Mathew *et al*, 2006). The majority of these findings were from large multi-centre trials, however a similar pattern of transient decrement in HRQoL has also been described in observational cohorts (Kang *et al*, 2005; Hollander, Foster & Weiland, 2006; Sinakos *et al*, 2010; Marcellin *et al*, 2011; Matsushita *et al*, 2014) and in HIV/HCV co-infection (Thein *et al*, 2007; Kemmer *et al*, 2012; Mandorfer *et al*, 2014).

With the arrival of Direct Acting Antivirals (DAAs), HRQoL data has begun to be reported timeous alongside biomedical end points. The polymerase inhibitor sofosbuvir was the first drug to have PEG-IFN free regimens reported in relation to HRQoL, which show significantly less impairment during therapy, although a modest decrement still remains during the 12 week treatment duration (Younossi *et al*, 2014a; Younossi *et al*, 2014b). As this data is exclusively from clinical trials it remains to be seen whether a similar scenario is observed in a patient population more representative of a typical clinical cohort; for example one including active substance users.

HRQoL Post-Treatment

For patients who achieve an SVR, benefits of treatment have been reflected in improvements to fatigue, and both physical and mental health domains of their HRQoL (Table 3). The domains in which improvements are reported are not consistent however,

and indeed some studies have reported HRQoL remains significantly impaired following viral clearance with interferon therapy (e.g. Tillmann *et al*, 2011). With the differences between results from the reported studies, it is important to examine the various limitations that may have influenced these findings.

The time-point at which post-treatment HRQoL is measured could potentially influence the results obtained. For example, Pojoga *et al* (2006) concluded that antiviral therapy does not improve HRQoL, however their post-treatment measurement was taken immediately after therapy had finished. In contrast, a cross-sectional study by John-Baptiste *et al* (2009) reported that patients who had achieved an SVR had improved HRQoL at an average of 3.7 years post-therapy. The majority of studies have measured for improvement in HRQoL at 24 weeks post end of treatment, a time when Helbling *et al* (2008) note that the positive emotional response due to treatment success is still strong and possibly influences responses. More recently, measurement of SVR at week 12 post-treatment has been accepted as a primary end point for most clinical trials (Chen *et al*, 2013) with HRQoL data also collected at this time-point, possibly when the emotional response is even stronger, or the effects of treatment are still being felt.

Another frequently reported limitation in the literature is that of patient awareness of their serological result prior to completion of the psychometric tools; do patients *feel* better, simply because they know they have now cleared the infection? McHutchison *et al* (2001) argued that as changes in HRQoL are seen in different domains and not reported 'across-the-board', it was unlikely that awareness of SVR was entirely responsible for the observed improvements. A later study which blinded serological results to patients and investigators found improvements in mental health for patients who had undetectable HCV RNA at week 12 of therapy compared to those who remained detectable (Quarantini *et al*, 2008), supporting the theory that knowledge of cure cannot account for all HRQoL increases alone.

As shown, the quantitative literature deals primarily with HRQoL cause and effect, reducing the burden of illness to numeric estimates which may demonstrate statistical and clinical significance, but the true patient experience, and the patient voice, remains silent. It is with this in mind that we turn to the qualitative literature, and examine the main themes present in that body of work, beginning with the experience of diagnosis.

Diagnosis

A number of studies have drawn on the theory of chronic illness as biographical disruption (Bury, 1982) to provide insight into their participants' narratives of diagnosis. Medically, HCV is defined as a chronic infection if it does not spontaneously resolve within the first 6 months following acquisition (Seeff, 2002), however socially-constructed chronicity refers to a state of long-term pain and suffering that may not be 'cured' (Martin & Peterson, 2009). For many, an initial reaction of shock was accompanied by overwhelming feelings of fear, denial, anger and depression following their HCV diagnosis (Glacken, Kernohan & Coates, 2001; Tompkins, Wright & Jones, 2005; Sutton & Treloar, 2007; Groessl *et al*, 2008; Janke *et al*, 2008; Sgorbini, O'Brien & Jackson, 2009; Olsen, Banwell & Dance, 2012). Faye & Irurita (2003) describe their participants feeling condemned, with their futures being forfeited:

"It was a death sentence. Not knowing a lot about it, and asking my doctor if I was going to die in ten years and he couldn't tell me" (Faye & Irurita, 2003 p.94)

In participants who had a history of injecting drug use, reactions to HCV diagnosis were sometimes modified and tempered, either because they suspected they were HCV positive anyway (Temple-Smith, Gifford & Stoové, 2004; Olsen, Banwell & Dance, 2012), or because of multiple HCV diagnoses within their peer group around the same time, providing context and mitigating the impact (Fry & Bates, 2012). It also served as an unwelcome reminder of a previous time in their lives, potentially exposing an earlier identity that many had worked

hard to put behind them (Grundy & Beeching, 2004; Fry & Bates, 2012; Olsen, Banwell & Dance, 2012; Hill *et al*, 2014):

“I was thrown right back there and it was awfully upsetting because I really did think that that time of my life was past and that I’d come to terms with grief and difficulty and all sorts of things in my life. And what happened? The legacy...” (Fry & Bates, 2012 p.467)

For individuals who had been experiencing significant symptoms of HCV such as unexplained fatigue, the intensely negative reaction to their HCV diagnosis also came with a sense of relief as their health problems had finally been formally identified and medically labelled (Glacken, Kernohan & Coates, 2001; Copeland, 2004; Groessl *et al*, 2008). Importantly, the reaction of current IDUs to an HCV diagnosis appears to be significantly less traumatic; not conforming to Bury’s (1982) notions and perhaps representing more ‘biographical reinforcement’ (Carricaburu & Pierret, 1995) than ‘biographical disruption’. This will be discussed in greater detail in due course.

Following diagnosis, the re-evaluation of an individual’s life and an attempt to regain control are commonly reported. Diagnosis can serve as a catalyst for the re-examination of life’s priorities (Glacken, Kernohan & Coates, 2001), attempting to integrate HCV into a comfortable, acceptable and balanced future life (Faye & Irurita, 2003). A lack of information and understanding of HCV at diagnosis could hinder this process however, denying the sought after sense of control and exacerbating prognostic uncertainty (Glacken, Kernohan & Coates, 2001; Sutton & Treloar, 2007).

The Lived Experience of HCV: Fatigue

Fatigue is one of the most prevalent symptoms of HCV reported (Glacken, Kernohan & Coates, 2001; Glacken *et al*, 2003; Conrad *et al*, 2006; Groessl *et al*, 2008; Fry & Bates,

2012; Jiwani *et al*, 2013), and a greater understanding of how this impacts HRQoL starts to emerge when reviewing the qualitative data. The fatigue experienced has been described as discernible from 'normal fatigue' and multidimensional in nature, perniciously impacting on physical, cognitive and affective dimensions, creating a whole body feeling of fatigue which is unrelieved by rest (Glacken, Kernohan & Coates, 2001; Glacken *et al*, 2003):

"You cannot fight it; it is not a tiredness that you can fight like a normal tiredness. A normal tiredness, you can fight it and get a second wind or if you had a few cups of coffee, it would keep you going. None of this works with this tiredness" (Glacken *et al*, 2003 p.247)

The unpredictability of symptoms has also proved challenging. A number of studies describe sporadic and episodic experiences of HCV illness (Conrad *et al*, 2006; Sutton & Treloar, 2007) which have a high impact on life when they occur, but when absent almost serve to reinforce a notion that the virus is not currently affecting health (Swan *et al*, 2010).

The Lived Experience of HCV: Onward Transmission

The possibility of passing the virus onto others has evoked strong reactions in a number of studies, with some participants citing it as a far greater HRQoL issue than any physical symptoms experienced (Conrad *et al*, 2006). Women have discussed worries over vertical transmission to children (Temple-Smith, Gifford & Stoové, 2004; Conrad *et al*, 2006), which in addition to causing possible disruption to plans for a family, can also impact sex lives and relationships (Grundy & Beeching, 2004; Lenton *et al*, 2011; Jiwani *et al*, 2013). The knowledge that HCV is contagious, and subsequent fear of transmission to others, forms a large part of the psychological impact of living with HCV, eliciting constant feelings of anxiety and sadness (Hill *et al*, 2014).

The Lived Experience of HCV: Impact on Current IDUs

As previously mentioned, the reaction of current IDUs to an HCV diagnosis appears significantly less traumatic than those who stopped injecting many years ago and those who acquired HCV through another route. A lack of shock following the diagnosis (Faye & Irurita, 2003; Groessl *et al*, 2008; Harris, 2009) appears to be accompanied by a sense of inevitability linked to a high prevalence of HCV within their social networks (Sutton & Treloar, 2007; Olsen, Banwell & Dance, 2012; Hill *et al*, 2014). A commonly reported consequence of HCV diagnosis is an intense and overwhelming depression, however in current IDUs this has been described as shallow, and nothing to be dwelt on (Faye & Irurita, 2003) epitomised by a *“what’s done is done, I can’t change it now...”* (Tompkins, Wright & Jones, 2005, p.265) attitude. Davis & Rhodes (2004) note that HCV is constructed as something acquired rather than caught among the IDUs they interviewed in London, language that implies transmission is unavoidable, normalized and almost acquired over time; a ubiquitous risk. Wozniak *et al* (2007) explored this apparent normalization of HCV amongst IDUs in Canada, describing HCV as a defining characteristic of injecting drug use. Further work from Australia reiterates these perceptions, with one study participant articulating her experience:

“And nobody talked about hep C really. I mean you know, in passing, it was just so assumed everybody had it. And nobody saw it as a big deal. No-one was thinking about it. Nobody thought it was anything other than just a complete minor detail that had no bearing on life at all” (Harris, 2009 p.1032)

Roy *et al* (2007) suggest that an HCV diagnosis could actually have a positive significance for some, as it enables the individual to feel just like everyone else in their situation, or *“... one of the gang, like”* (Roy *et al*, 2007 p.400). These ambivalent views towards disease diagnosis are at odds with Bury’s (1982) account of biographical disruption, and instead appear to reinforce conceptions of self-identity and personal biography (Carricaburu & Pierret, 1995); HCV infection is synonymous with injecting drug use, and therefore injecting drug use will naturally lead to HCV infection (Olsen, Banwell & Dance, 2012).

HCV may also have limited impact on life, as the diagnosis can be lost in a sea of multiple disruptions. In work with IDUs in Edinburgh, Copeland (2004) describes apathy towards having HCV perhaps stemming from multiple traumas faced in day-to-day life, and the significance of being HCV positive eclipsed by problematic existences and their identity as a 'problem drug user'. If the severity of HCV in relation to other more immediate life-threatening conditions (such as overdose) is considered, health problems that may not develop for many years such as those linked to HCV are unlikely to be overly concerning or prioritised, and activities that seek to improve an unimaginable future, such as HCV treatment, are not options worth investing in (Roy *et al*, 2007). Williams (2000) astutely notes that biographical disruption is perhaps more keenly felt among the privileged rather than disadvantaged sections of society.

As well as being contextualised within an individual's life, a diagnosis of HCV is often described in relation to HIV/AIDS (Copeland, 2004; Davis & Rhodes, 2004; Cullen *et al*, 2005; Tompkins, Wright & Jones, 2005; Roy *et al*, 2007; Wozniak *et al*, 2007; Munoz-Plaza *et al*, 2008; Harris, 2009; Swan *et al*, 2010; Lekas, Siegel & Leider, 2011). HIV is often defined as the primary viral risk for injecting drug use, with the seriousness of HCV being undermined by HIV (Davis & Rhodes, 2004). Excerpts from studies showing participants reactions at diagnosis serve to highlight this point:

"I wouldn't mind but I was in bits waiting for the results...the doctor was there going 'now...you have hepatitis C.' I was there going 'hurry up and tell me about the (HIV) virus'" (Cullen *et al*, 2005 p.74)

"She told me 'everything looks fine, except it's written positive next to hepatitis C'. So I said to her, 'can I see? I hope I don't have AIDS'" (Roy *et al*, 2007 p.400)

Even in HIV/HCV co-infection, a diagnosis of HCV can be over-shadowed by already having HIV (Copeland, 2004; Lekas, Siegel & Leider, 2011). As public health harm-reduction messages for drug users historically centred on HIV prevention, HCV appeared within this framework later as an additional concern (Davis & Rhodes, 2004; Harris, 2009). This 'lesser of two evils' perception appears to pervade, with HCV presented as relatively benign in comparison to HIV, and cited as a reason why further investigations and treatment are not accessed post diagnosis (Swan *et al*, 2010).

The fact that HCV is often asymptomatic can also contribute to its low priority in lives with many competing demands. Although fatigue, cognitive impairment and depression are known symptoms, these are not ubiquitous, and where they do occur may not always be attributed to HCV, particularly where there is co-morbid active substance use. Due to the lack of physical impact there is no sense of threat from harbouring the virus (Fraenkel *et al*, 2005) and it therefore becomes an insignificant part of people's lives (Sutton & Treloar, 2007). Witnessing substance users 'living normally' and showing no signs of sickness can reinforce the normalization and social accommodation of HCV within social networks, psychologically and socially preparing other members for a potential diagnosis (Faye & Irurita, 2003; Carrier, LaPlante & Bruneau, 2005).

Reviewing these narratives as a whole, it could be easy to construe that all current substance users are disinterested in their health. However, despite repeated reports of an HCV diagnosis having little impact upon lives (Faye & Irurita, 2003; Sutton & Treloar, 2007; Olsen, Banwell & Dance, 2012), there are examples of individuals reacting badly to the news (Tompkins, Wright & Jones, 2005; Sutton & Treloar, 2007). For some, an overwhelming sense of contamination has been described accompanied by a response characterized by despair (Fraser & Treloar, 2006). Rather than focusing the individual to address the cause however (by potentially seeking treatment), a number of accounts relate a sense that the infection is now with them for life, and as such interest in their health may actually decrease:

“Oh what’s the use? You’ve got it, it’s not going to go away, what’s the use?” (Fraser & Treloar, 2006 p.106)

“What’s the point? I’m either going to die from drugs or from liver disease” (Groessler *et al*, 2008 p.1961). The authors note that immediately after diagnosis this participant began using drugs again.

The Lived Experience of HCV: Stigma

The preponderance of accounts detailing individuals’ experience of stigma in relation to HCV, create an overriding and pervasive theme within the literature on life experience, and again highlight its relative absence from the quantitative work. The stigma experienced is multifaceted, incorporating a number of factors including the involvement of an infectious agent (Faye & Irurita, 2003; Conrad *et al*, 2006; Fraser & Treloar, 2006) and an association with HIV/AIDS (Zickmund *et al*, 2003), however the most frequently described association is with illicit injecting drug use (Faye & Irurita, 2003; Zickmund *et al*, 2003; Conrad *et al*, 2006; Paterson *et al*, 2006; Butt, Paterson & McGuinness, 2008). This link to substance use is persistent and tenacious, and stigma and discrimination related to substance use have been experienced by many individuals with HCV irrespective of their mode of acquisition (Faye & Irurita, 2003; Butt, Paterson & McGuinness, 2008; Fry & Bates, 2012; Hill *et al*, 2014):

“We are all tarred with the same brush. People think ‘hepatitis’, yeah they’re all drug addicts, and they think ‘they’ve done something wrong’” (Hill *et al*, 2014 p.5)

These stigmatising attitudes are encountered from family, friends, colleagues and also frequently within the healthcare setting (Miller, Hiller & Shaw, 2001; Zickmund *et al*, 2003; Grundy & Beeching, 2004; Temple-Smith, Gifford & Stoové, 2004; Tompkins, Wright & Jones, 2005; Butt, Paterson & McGuinness, 2008; Janke *et al*, 2008; Sgorbini, O’Brien &

Jackson, 2009; Fry & Bates, 2012; Jiwani *et al*, 2013; Hill *et al*, 2014). Accounts from the literature also demonstrate an internalised stigma, whereby HCV positive individuals assimilate these widely held social views and describe feeling contaminated, dirty or 'like a leper' (Glacken, Kernohan & Coates, 2001; Miller, Hiller & Shaw, 2001; Zickmund *et al*, 2003; Grundy & Beeching, 2004; Fraser & Treloar, 2006; Sutton & Treloar, 2007; Hill *et al*, 2014).

A decision not to disclose HCV positive status is often borne out of fears around subsequent stigmatisation (Glacken, Kernohan & Coates, 2001; Faye & Irurita, 2003; Tompkins, Wright & Jones, 2005; Conrad *et al*, 2006; Fraser & Treloar, 2006; Sutton & Treloar, 2007; Butt, Paterson & McGuinness, 2008; Sgorbini, O'Brien & Jackson, 2009; Jiwani *et al*, 2013; Hill *et al*, 2014), and can have a substantial impact on people's lives, for example by not identifying oneself as HCV positive, the opportunity to obtain support is lost (Faye & Irurita, 2003; Hill *et al*, 2014). In addition, any causal explanation for symptoms being experienced is removed, meaning individuals may have to continue working whilst extremely fatigued, or deny any emotional stress they may be suffering (Butt, Paterson & McGuinness, 2008; Fry & Bates, 2012):

"It requires a constant vigilance on my part not to let it slip...you always have to appear 'normal' regardless of how you are really feeling" (Glacken, Kernohan & Coates, 2001 p.110)

Non-disclosure can have more wide reaching implications. Butt, Paterson and McGuinness (2008) describe how one participant in their study quit his job and withdrew socially to conceal the diagnosis and associated symptoms. Although this voluntary social withdrawal may seem an extreme reaction, it serves to illustrate the impact of deep-seated and entrenched discrimination towards individuals with HCV which pervades unchanged throughout the historic literature up to the present day. Clearly, social isolation is not purely

a voluntary undertaking however, and Glacken, Kernohan and Coates (2001) describe the diagnosis of HCV resulting in participants feeling their 'social identity' had been stripped away, preventing them from maintaining previous social relationships.

The Experience of HCV Treatment

In addition to offering valuable insights into how HCV impacts on day-to-day life, the qualitative research also explores how the transient decrement in HRQoL reported in the quantitative literature is experienced, illustrating its impact on daily life and offering a greater depth of understanding. The side-effects of IFN-based therapy are expounded with a clear patient voice, illuminating their intense and persistent nature and contextualising their impact on the individual. These side-effects compromise employment opportunities and contribute to absenteeism (Hopwood & Treloar, 2005), affect physical appearance and changes in demeanour resulting in altered perceptions by others (Sheppard & Hubbert, 2006), and contribute to social isolation (Janke *et al*, 2008). The persistence of these symptoms throughout the course of treatment, and the unpredictability of onset are also significant factors contributing to the reduced HRQoL experienced (Fraenkel *et al*, 2006).

With insights into the lived experience of treatment and its side-effects, understandings into how these symptoms are managed and strategies for coping are also illuminated. Hopwood & Treloar (2008) focused on Resilience Theory, describing participants drawing on past experience of drug dependence, their history and experience of living with a chronic illness and challenges and lessons learned from a socially disadvantaged life. This theory is borne out in other studies, with examples of patients undergoing HCV treatment relating their use of anger management techniques learned at an alcohol treatment centre (Taylor-Young & Hildebrandt, 2009), and eschewing HCV support groups in favour of more familiar 12-step programmes previously attended (Sheppard & Hubbert, 2006). In addition to resilience, support from friends and family is also a key factor in adherence to and continuation of treatment (Sgorbini, O'Brien & Jackson, 2009; Swan *et al*, 2010; Chapman & McManus,

2012), with recurrent reports of strong family support not uncommon in the literature (Sheppard & Hubert, 2006; Jiwani *et al*, 2013; Manos *et al*, 2013), although a mixture of positive and often very negative experiences in relation to friends and family are frequently described.

Discussion

As the experience of illness and treatment from the patient perspective continues to gain importance, this review has endeavoured to demonstrate the value of considering patient-reported outcome measures from a variety of sources. Psychometric instruments describe the health status of individuals at specific time points, providing valuable data to satisfy drug licensing requirements, and also providing quantifiable and accessible insights into HRQoL. These are beneficial for assessing cost utility and thus the economic benefits of an intervention. However, much of this evidence comes from large randomised controlled trials (RCTs), whose participants are often unrepresentative of the larger HCV population, undermining ecological validity and generalizability (Britton *et al*, 1999; Van Spall *et al*, 2007). To illustrate this point, Beinhardt *et al* (2012) examined whether selection bias was observed within their clinical centre for patients who underwent HCV treatment through an RCT. Those enrolled to an RCT had less advanced liver disease, less frequent history of psychiatric disorders and were less likely to be prescribed opioid-substitution therapy compared with those receiving routine care, which was largely driven by the studies exclusion criteria. In another example, in a large RCT for patients being treated with telaprevir, Vera-Llonch *et al* (2013) reported trial participants' baseline EQ-5D scores were actually higher than published US population norms making them not only unrepresentative of the HCV population, but of the general population as well. These types of selection bias conspire to present evidence for HRQoL obtained under 'ideal' conditions, with far fewer reports on the effect in 'real-world' populations with HCV.

In addition to concerns regarding generalizability, there are also methodological difficulties with psychometric questionnaires measuring HRQoL. Individuals with low literacy skills are frequently excluded from studies that develop and validate self-completed questionnaires (Jahagirdar *et al*, 2013) and within the field of HCV this has particular relevance, as it is estimated that up to 90% of those infected are current or former substance users (Hutchinson *et al*, 2006) who typically fall into this category. The use of psychometric questionnaires has not therefore been validated in actively substance-using populations (Dalgard *et al*, 2004). Further methodological difficulties including the complexity of choosing the correct tool, the lack of standardization across a condition-specific field, and the extent to which the chosen tool covers the concept being investigated have also been reported (Refolo *et al*, 2012). For example, recent trials using direct acting antivirals in the treatment of HCV administered four separate questionnaires to their patients; a generic HRQoL survey, a disease-specific HRQoL survey, a questionnaire assessing the impact of fatigue, and one investigating impairment in daily activities and work productivity (Younossi *et al*, 2014a). The sheer volume of paperwork involved in completing these questionnaires, and the time and concentration required to do so questions the quality of the information collected. In addition, questionnaires may not capture the most pertinent concerns of the patient. These instruments do not elucidate what strategies are employed by people to cope with any decrements to HRQoL they may experience, or explore the impact on behaviour and functioning in wider society.

The qualitative literature therefore not only complements the quantitative HRQoL data, but also aids its interpretation. For example, the insights gained into how HCV is viewed as a chronic illness help explain the variation in HRQoL observed in quantitative studies. If living with HCV is considered along a chronic illness continuum, then a deeper insight into varying responses to psychometric assessments which are made at specific points in time is gained. Without this insight, it could be argued that compiling these responses and effectively reporting a 'mean value' has limited relevance and clinical application. Indeed, this

approach also masks the disparity of reactions to diagnosis amongst current IDUs and other groups illuminated by the qualitative paradigm; a lower HRQoL is not necessarily *experienced* in the same way by all those it affects, which may have significant implications for engagement in treatment services. Further, without accounting for the social stigmatisation HCV elicits (Paterson *et al*, 2007), the findings of most questionnaire-based HRQoL research are left open to conjecture. Qualitative studies give a recognisable voice to the decrements and improvements in HRQoL described in the quantitative work, in addition to revealing more nuanced and deeper insights which also have important clinical significance. The two bodies of research are therefore not only complementary, but essentially interconnected; the depth of understanding of the true burden of illness is absent unless qualitative accounts of the lived experience are reviewed concurrently alongside quantitative research. An equivalent value should therefore be applied to this body of work; however there is a distinct disparity between their relative authorities.

Quantitative HRQoL data is highly valued by policy makers, however reference to qualitative HRQoL research is largely absent from clinical management guidelines. The Scottish Intercollegiate Guidelines Network (SIGN) (2013) reference HRQoL only once in their HCV management guidelines. The European Association for the Study of the Liver (EASL) (2014) also contain one citation; and the American Association for the Study of Liver Diseases (AASLD & IDSA, 2014) address the issue briefly, but in slightly more detail through the context of extra-hepatic manifestations of HCV such as fatigue. In documents aimed at guiding clinical practice, the omission of any significant input from HRQoL data highlights their medical focus; these are guidelines for the management of the hepatitis C virus, not the care of the patient.

All of these guidelines are designed to assist clinical decision-making in order to optimise the management of HCV patients, however do so with little focus on how that management may affect the individual's life, or indeed what the HCV positive individual's priorities may actually

entail. This seems contradictory to the biopsychosocial model of care; in which recommendations encompassing the management of the virus, should be combined with recommendations for humane treatment. Addressing the impact of HCV on an individual's HRQoL is perhaps as valuable as knowing the most efficacious drug combination to treat the virus, yet this focus is effectively absent from clinical guidance. Some bodies, such as The Australasian Hepatology Association (2012) have produced nursing guidelines which begin to address this issue, however a more global multidisciplinary initiative would contribute to ensuring that HCV care remains patient-focused, and not entirely results driven in an age of care characterised by drug development. It is also possible that as the influx of new treatments for HCV continues, decision-makers may ask that drugs be assessed not only on clinical efficacy or economic efficiency but also on humanistic outcomes (Gao *et al*, 2012).

As with all syntheses of research, there are limitations to this review. There is the possibility that relevant literature has been inadvertently omitted, however the search strategies aimed to account for this through the use of multiple databases and broad search terms.

Publication bias may be evident due to the inclusion of interventional studies in the quantitative arm, however discussion of the limitations of these has been made, and to exclude these from the review could itself lead to a narrative bias considering their abundance within the literature. To ensure all included articles were peer-reviewed, unpublished works were not included. Within the qualitative narrative, the included studies were conducted in different settings with a diverse group of participants, however the identification of broad key themes purposefully aimed to transcend these limitations and focus on shared insights. Finally, as previously mentioned, the variation in how drug use is reported within the published literature, and the lack of consensus on what constitutes 'substance use' or 'drug abuse', and poor definition of the terms 'active', 'current' or 'previous' drug use is problematic. For the purposes of this review, supplementary files 1 and 2 make explicit the inclusion criteria stated in individual studies, however further clarity around this matter would benefit the interpretation of this literature as a whole.

Conclusion

Whilst the quantitative literature continues to report contemporary data on HRQoL with new treatment regimens (e.g. Younossi *et al*, 2014a), only one qualitative study reporting patient perspectives on HCV treatment since the advent of triple therapy has been published to date (Rasi *et al*, 2014), and as such a rounded contemporary understanding of HRQoL for individuals with HCV is absent. This review aims to catalyse further qualitative research in this area and to provoke discussion into the greater use of all HRQoL data within the development of clinical practice guidelines.

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Figure 1: Flowchart of included and excluded studies identified in the quantitative search strategy.

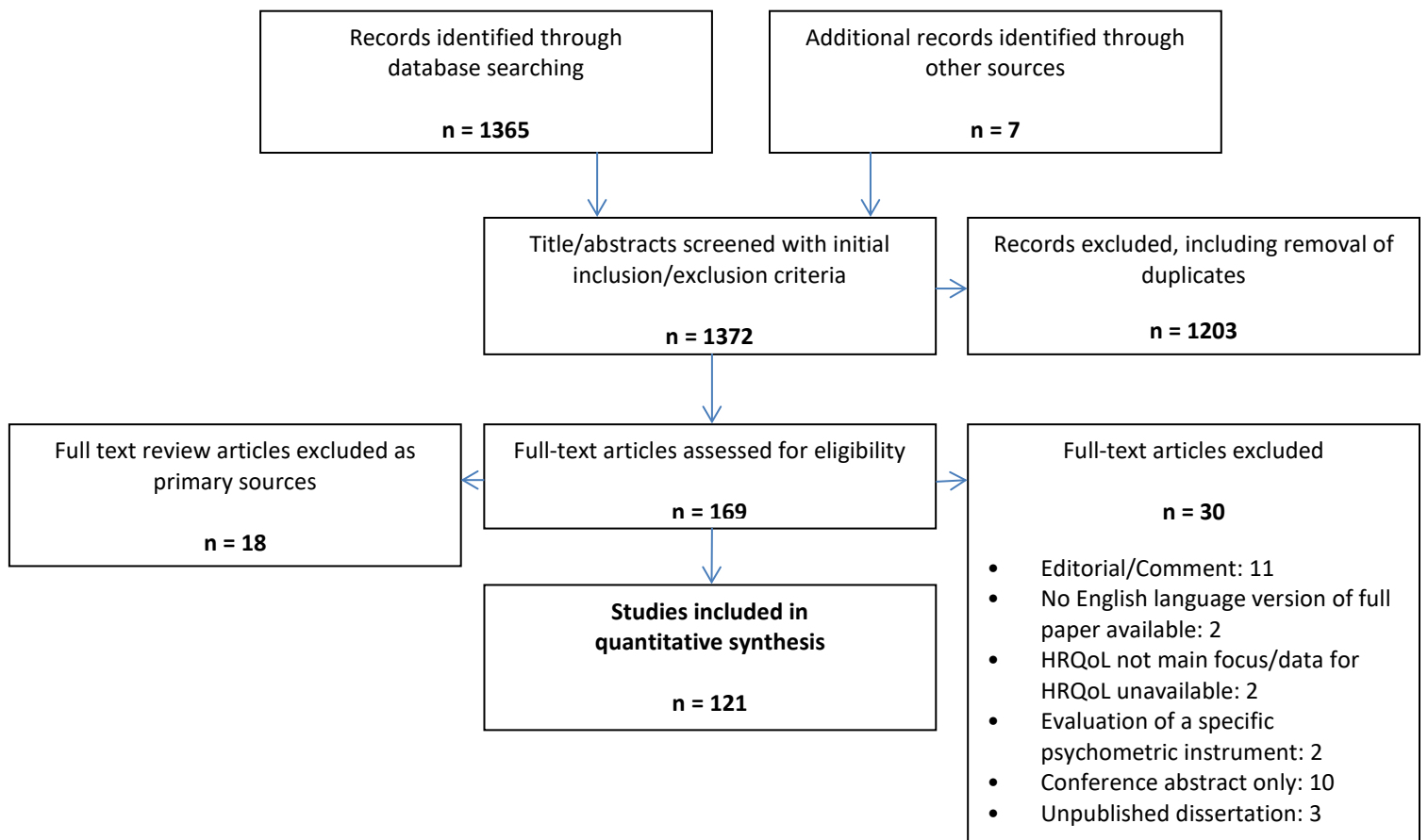


Figure 2: Flowchart of included and excluded studies identified in the qualitative search strategy

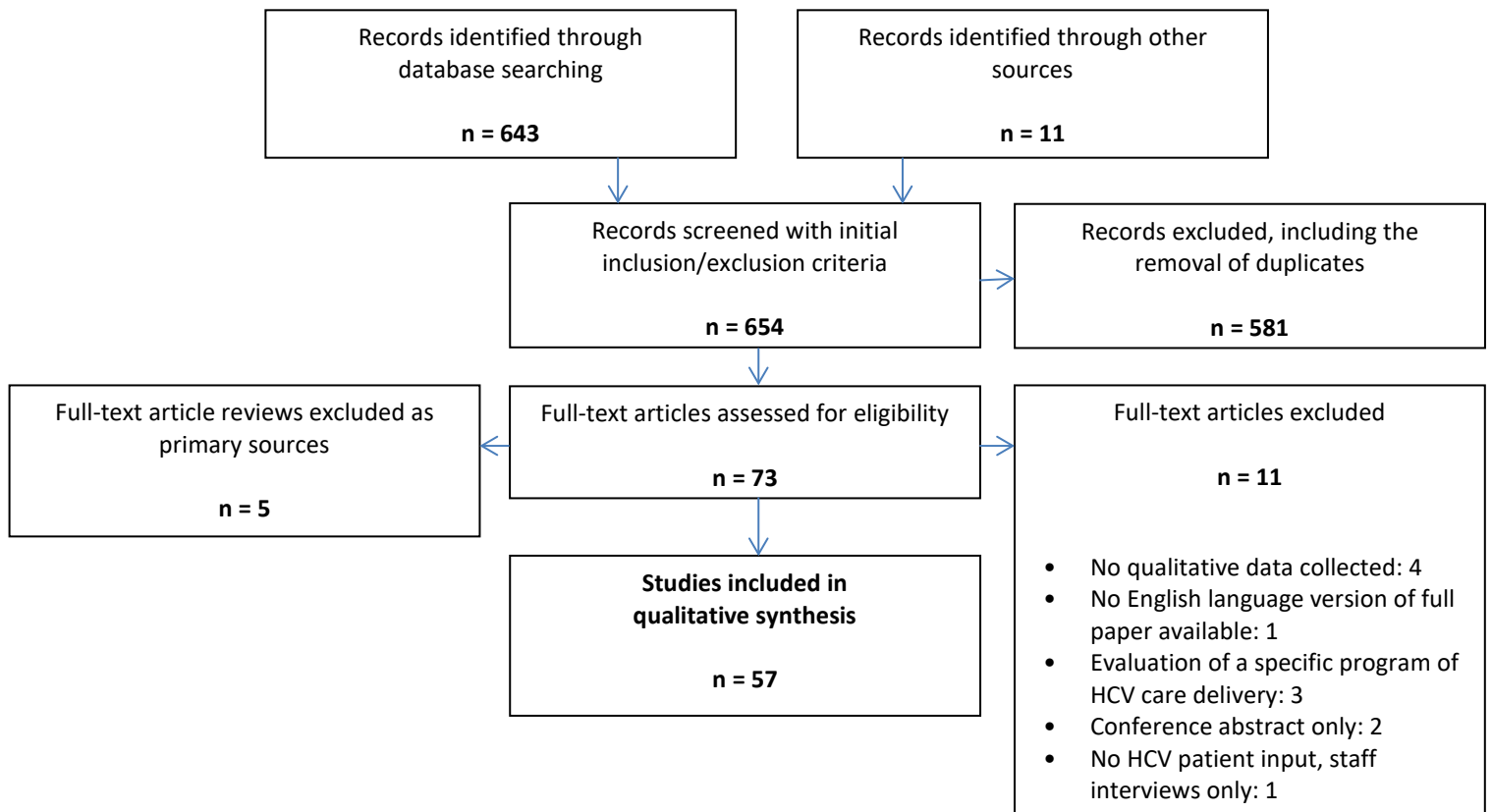


Table 1: Example of the electronic search strategy used within the Medline database for both the quantitative and qualitative search strategies. No limits were applied, searches last conducted on 29.09.2014.

	Quantitative Search Strategy	Number of Studies	Qualitative Search Strategy	Number of Studies
Search Terms (ST) or Subject Index Terms (SIT)	S1: Hepatitis C (SIT), OR Hepatitis C, Chronic (SIT) OR Hepatitis C (ST)	66,420	S1: Hepatitis C (SIT), OR Hepatitis C, Chronic (SIT) OR Hepatitis C (ST) AND Quality of Life (SIT) OR Quality of Life (ST) OR Life Change Events (SIT) OR Experience (ST)	2,248
	S2: Patient Outcome Assessment (SIT) OR Patient Reported Outcomes (ST) OR Quality of Life (SIT) OR Health-Related Quality of Life (ST) OR HRQL (ST) OR HR-QOL (ST) OR HRQOL (ST)	65,897	S2: Qualitative Research (SIT) OR Qualitative (ST) OR Interview, Psychological (SIT) OR Interview as Topic (SIT) OR Interview* (ST)	348,448
	S3: S1 AND S2	319	S3: S1 AND S2	133
	Application of initial inclusion/exclusion criteria	136	Application of initial inclusion/exclusion criteria	43
	Further exclusions following retrieval of full articles	121	Further exclusions following retrieval of full articles	36
	Number of studies excluding reviews	106	Number of studies excluding reviews	34

Table 2: Summary of all studies identified within the quantitative search arm (see supplementary file 1) where the most commonly used tool was employed (SF-36), and data reported for HCV patients versus ‘healthy’ controls or population norms in the 8 SF-36 subscales is available. ‘S’ indicates a reported statistically significant impairment compared with healthy controls or population norms.

Author & Year	n =	SF-36 Subscales							
		Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role-Emotional	Mental Health
Bayliss <i>et al</i> (1998)	157	S	S	S	S	S	S	S	S
Foster <i>et al</i> (1998)	72	S	S	S	S	S	S	S	S
Bonkovsky <i>et al</i> (1999)	642	S	S	S	S	S	S	S	S
Ware <i>et al</i> (1999)	324	S	S		S	S	S		
Bianchi <i>et al</i> (2000)	126		S		S	S	S	S	S
Fontana <i>et al</i> (2001)	107	S	S	S	S	S	S		S
Hussain <i>et al</i> (2001)	220	S	S	S	S	S	S	S	S
McHutchison <i>et al</i> (2001)	912	S	S		S	S	S		
Miller <i>et al</i> (2001)	95	S	S	S	S	S	S	S	S
Kramer <i>et al</i> (2002)	100	S	S		S	S	S	S	S
Córdoba <i>et al</i> (2003)	120	S	S	S	S	S	S		
Gallegos-Orozco <i>et al</i> (2003)	157	S	S	S	S	S	S	S	S
Dalgard <i>et al</i> (2004)	199	S	S	S	S	S	S	S	S
Fleming <i>et al</i> (2004)	299	S	S	S	S	S	S	S	S
Kang <i>et al</i> (2005)	182	S	S		S	S		S	S
Kramer <i>et al</i> (2005)	120	S	S	S	S	S	S	S	S
Rowan <i>et al</i> (2005)	62	S	S		S	S		S	
Balfour <i>et al</i> (2006)	123	S	S	S	S	S	S	S	S
Danoff <i>et al</i> (2006)	112	S	S	S	S	S	S	S	S
Gjeruldsen <i>et al</i> (2006)	42	S	S		S	S	S	S	S
Hollander <i>et al</i> (2006)	147	S	S	S	S	S	S	S	S
Lim <i>et al</i> (2006)	201				S		S	S	S
Mathew <i>et al</i> (2006) 'responders'	25								
Mathew <i>et al</i> (2006) 'non-responders'	130	S	S	S	S	S	S		
Pojoga <i>et al</i> (2006)	35	S	S	Excluded	S	S	S	S	S
Thein <i>et al</i> (2006)	267				S		S	S	S
Bonkovsky <i>et al</i> (2007)	1144	S	S	S	S	S	S	S	S
Kallman <i>et al</i> (2007)	130	S	S	S	S	S	S	S	S
Taliani <i>et al</i> (2007) 'non-responders'	58		S	S	S	S	S	S	S
Taliani <i>et al</i> (2007) 'relapsers'	43		S		S		S	S	
Taliani <i>et al</i> (2007) 'untreated'	163				S	S			
Teixeira <i>et al</i> (2007) 'no liver biopsy'	37			S	S		S	S	S
Teixeira <i>et al</i> (2007) 'liver biopsy'	40		S	S	S	S	S	S	S
Teixeira <i>et al</i> (2007) 'for treatment'	43	S	S	S	S	S	S	S	S
Helbling <i>et al</i> (2008)	833	S	S	S	S	S	S	S	S
Kwan <i>et al</i> (2008)	303		S	S	S	S	S	S	S
Batki <i>et al</i> (2009)	100	S	S	S	S	S	S	S	S
Björnsson <i>et al</i> (2009)	472		S		S	S	S	S	S
Hsu <i>et al</i> (2009)	271	S	S	S	S	S	S	S	S
Karaivazoglou <i>et al</i> (2010)	39	S	S	S	S	S	S	S	S
Sinakos <i>et al</i> (2010)	99		S		S		S	S	
Chang <i>et al</i> (2014)	108		S		S	S	S	S	S
Kuwashiro <i>et al</i> (2014)	175				S				
Matsushita <i>et al</i> (2014)	228		S		S				
Strauss <i>et al</i> (2014)	35	S		S	S	S	S	S	S

Table 3: Summary of all studies identified within the quantitative search arm (see supplementary file 1) comparing HRQoL in HCV patients (as measured by SF-36 or HQLQ) who achieve SVR compared to their baseline levels or non-responders. Only studies where data for SF-36/HQLQ subscales has been reported are included. 'S' indicates a reported statistically significant improvement compared to baseline levels or non-responders, 'T' indicates a trend towards (*indicates SVR12 reported).

Author & Year	n =	Clinical Trial Data?	SF-36 Subscales								SF-36 Summary Scales		HQLQ Additional Domains			
			Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health	PCS	MCS	Sleep	Health-Distress	CHC Health-Distress	CHC Limitations
Bonkovsky <i>et al</i> (1999)	642	✓	S	S		S	S	S								
Ware <i>et al</i> (1999)	324	✓				S	S	S					S	S	S	
McHutchison <i>et al</i> (2001)	912	✓	S	S			S	S								
Bernstein <i>et al</i> (2002)	1441	✓	S	S	S	S	S	S	S	S	S	S				
Desmorat <i>et al</i> (2003)	168		S	S	S	S	S	S	S	S	S	S				
Rasenack <i>et al</i> (2003)	531	✓	S	S		S	S	S		S	S	S				
Hassanein <i>et al</i> (2004)	1121	✓	S	S	S	S	S	S	S	S	S	S				
Perillo <i>et al</i> (2004)	412	✓									T	T				
Kang <i>et al</i> (2005)	182		S	S	S	S	S	S	S	S						
Arora <i>et al</i> (2006)	491	✓	S	S	S	S	S				S					
Bini & Mehandru (2006)	92		S	S	S	S	S	S	S		S	S	S	S	S	S
	46		S	S		S	S	S	S	S	S	S	S	S	S	S
Dan <i>et al</i> (2006)	271					S										
Hollander <i>et al</i> (2006)	147			S		S	S	S			S					
Mathew <i>et al</i> (2006)	25	✓						T								
Pojoga <i>et al</i> (2006)	35															
Bonkovsky <i>et al</i> (2007)	1144	✓		S		S	S			S	S					
Thein <i>et al</i> (2007)	34		S	S		S	S	S	S	S	S	S				
John-Baptiste <i>et al</i> (2009)	235		S	S	S	S	S	S	S	S	S	S	S	S	S	S
Sinakos <i>et al</i> (2010)	99			S	S	S	T	S	S	S						
Marcellin <i>et al</i> (2011)	1860										S	S				
Bezemer <i>et al</i> (2012)	128	✓				S		S								
Isaacs <i>et al</i> (2013)	118		S	S		S		S						S	S	
Jerkeman <i>et al</i> (2014)	40															
Younossi <i>et al</i> (2014a)*	192	✓						S								
Younossi <i>et al</i> (2014b)*	278	✓							S							
	215	✓			S	S					T					
	201	✓	S	T	S		S				S					
	327	✓				S	S			S						
Younossi <i>et al</i> (2014c)*	334	✓				S	S				S					

