



Priority setting of future research into long-term symptoms of Covid-19 infection

Post-acute sequelae of Covid-19 or Long Covid

Prioritering baserat på James Lind Alliance metod

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Summary

Aim

What research topics matter most to people who have suffer post-acute sequelae of Covid-19 (Long Covid), relatives, clinicians and researchers within the field? The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) has made an inventory of research topics and invited relevant stakeholders to prioritize, these topics. In the project, long-term symptoms are defined as follows: the condition ”Long-term symptoms of Covid-19” refers to all forms of long-term disease, symptoms, complications and persistent discomfort, associated with Covid-19.”

The aim of the report is to help ensure that questions which are considered particularly urgent will be addressed by well-conducted and relevant research. This can apply both to research in the form of individual new studies, so-called primary research, and in the form of systematic reviews, in which the results of all studies within a specific field are critically appraised and summarized. The main target groups for the report are researchers, the bodies which fund research and authorities and organisations which compile research findings, international and Swedish.

Background

In 2020, SBU was commissioned by the Swedish Government to evaluate the scientific evidence of care for patients with long-term symptoms or sequelae (Long Covid) of the disease Covid-19. The report was published on December 1st, 2020. One of the directives of the commission was to summarize not only published studies but also currently ongoing studies. As Covid-19 is such a novel disease and research to date has focused primarily on treatment of the

acute phase of the infection, there are many aspects of long-term symptoms of the disease which require further research. SBU therefore decided to investigate which questions were considered most urgent by patients suffering long-term symptoms of Covid-19, relatives and clinicians and researchers, hence the initiation of this project. As it is unlikely that all research questions will be answered, there is always, conscious or unconscious, a process of prioritising in selecting research topics. This prioritising is usually done from the point of view of researchers, research funding agents (which may include a community perspective) and commercial interests, but seldom from the perspectives of the patients, relatives and clinicians, as to what they consider to be important. In this report we have asked what all these groups jointly consider should be prioritised.

Method

The priority setting process is based on a method developed by the James Lind Alliance. Patients, their relatives or closely connected, clinicians, and other relevant stakeholders are invited to nominate the research questions which they consider, from their perspective, to be important. In the current project researchers were also included even though this is not commonly the case. Clinicians in the current project refers to different professional groups who may be involved with these patients through their work, such as medical doctors, registered nurses, occupational therapists, physiotherapists, psychologists, enrolled nurses and dieticians. The method has an inclusive perspective, with equitable inclusion of the participants, whereby a mutual result is achieved on consensus principles. The method is not intended to produce an absolute truth, but the aim is to broaden the research perspective.

During the project, proposed research questions were collected by means of a questionnaire on SBU's website.

The priority setting was then undertaken by a working group, starting with two web-based questionnaires, followed by six final priority setting meetings, conducted digitally. The working group participants were recruited through an open interest notification on SBU's website.

Results

In response to the inventory questionnaire, 1,483 research questions were suggested in total, from 508 individuals. After exclusion of questions which were beyond the scope of the enquiry and combining questions on a similar theme, the result was a list of 97 comprehensive, overarching questions included in priority questionnaire 1.

In all, 553 people notified their interest in participating in the priority setting. Most were people with personal experience of the long-term symptoms of Covid-19. In two successive questionnaires, each participant was requested to select up to ten of the questions which mattered most to them. The results were weighted by perspective, so that all perspectives were included, with those questions they considered should have highest priority carried forward to the next stage.

In total, six separate digital priority setting meetings were held, with 29 participants in all, representing the various perspectives. At each meeting, the participants discussed the remaining 25 questions and came to general agreement as to which questions, they considered were the ten most important. SBU then combined the results of these six meetings to create a final top list (Table 1). All project participants have been given the opportunity to read and comment on the final list.

Several mutual ideas were presented during the six priority setting meetings. This included the proposal that research into why certain people are afflicted with long-term symptoms and the underlying cause to why certain symptoms arise, would provide fundamental knowledge on which treatment studies could be based. Furthermore, participants emphasised research questions which could contribute to improved knowledge, both for those who currently have symptoms and for those at risk (preventive measures). A more detailed description of the reasoning and motivation underlying this prioritising is to be found in Chapter 4 of the report.

The order of questions in the top list does not necessarily reflect the order in which the research should be carried out: it is merely listed in the order of what questions which was considered most important to answer. As several of the questions are broad, several studies may be required to answer them.

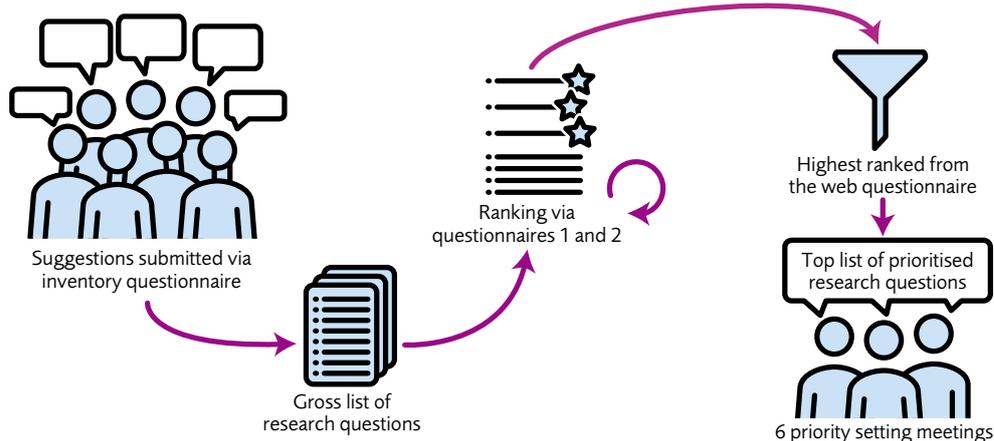


Figure 1 Schematic illustration of the design of the project.

Table 1 Top 10 list

Top 10 list of prioritised research questions about long-term symptoms of Covid-19 (1 = highest ranking).	
1	<p>What treatment is effective against persistent neurological symptoms and cognitive disturbances (such as brain fog, memory loss, difficulty concentrating, fatigue, numbness, tremor, headache) associated with Covid-19?</p> <p>How can rehabilitation efforts after long-term symptoms of Covid-19 be optimised and what measures should be included (occupational therapy, physiotherapy, psychology, social worker, speech therapist, dietitian etc.)?</p>
3	<p>What is the most effective treatment for long-term impaired breathing function/ oxygen uptake or problems with respiratory arrest, associated with Covid-19?</p>
4	<p>Why do certain people develop long-term symptoms of Covid-19?</p>
5	<p>How can an objective diagnosis be made of people with long-term symptoms of covid-19, regardless of whether they have had a positive PCR test during the acute phase, or if they have demonstrable antibodies?</p>
6	<p>Can expanded diagnosis, to investigate which organs are involved, result in better treatment and eventually prevent future complications in people with long-term symptoms of Covid-19?</p>
7	<p>What is the underlying cause of the various patterns of symptoms in people with long-term symptoms of covid-19?</p>
8	<p>What treatment can be given during the acute phase to prevent the development of long-term symptoms of Covid-19?</p> <p>What clinical manifestations occur in persons affected by long-term symptoms of Covid-19?</p>
10	<p>Is the immune response (e.g. T-cell response, antibodies to Covid-19, development of autoimmunity) different in people with long-term symptoms of Covid-19?</p>

Discussion

In this project, priority setting of research questions is based on consensus principles, whereby the participants, through questionnaires and meetings, reach mutual agreement on the results. The strength of the method is the inclusive perspective whereby patients, relatives, clinicians, and researchers are equal participants. A prerequisite for the method is that the knowledge and experience of each participant is acknowledged and regarded as having equal value.

Researchers do not usually participate in this type of project: there may be some conflict of interest, whereby they prioritise their own research. In this project however, we decided to include researchers under the same conditions as the other participants. This was partly because Covid-19 is a novel disease and many of the researchers within the field are also clinicians treating Covid-19 patients. To date they have most experience of the issues affecting people with long-term symptoms of Covid-19.

The priority setting covers a broad field and includes everything from basic research, to correlation studies, organisational issues as well as treatment studies. The SBU report on which the work is based, was however limited to investigation of symptoms, treatment and rehabilitation of long-term symptoms of Covid-19. However, as this field of research is so active, collations of research becomes outdated very fast. It is therefore important that researchers document the collected knowledge in this field before they embark on further research, including these questions of high priority. It is also important that in future, the published studies are collated and evaluated in systematic reviews.

The report was reviewed by SBU's internal quality assurance group, SBU's scientific advisory board and external reviewers.

1 Introduction

1.1 Aim

The report is intended to help ensure that well-conducted and relevant research is undertaken into long-term symptoms of Covid-19, on questions which are considered particularly important. This priority setting has been undertaken by people who are directly affected by research outcomes (patients, relatives, clinicians and researchers). The priority setting is based on a consensus method, which is intended to identify the questions which these groups mutually consider to be the most urgent topics for research. Identifying and disseminating information as to which research topics are considered to be the most important improves the potential for initiation of research on these topics.

SBU, the Swedish Agency for Health Technology Assessment and Assessment of Social Services, SBU is an independent national authority, tasked by the government with assessing health care and social service interventions from a broad perspective, covering medical, economic, ethical and social aspects. The process of scrutiny is a collaborative effort between SBU and leading experts. SBU is also required to systematically identify and actively present information about methods used in health and medical care and social services, for which there is uncertainty about the effects, so called evidence gaps.

Fact box 1 SBU's directive.

1.2 Target groups

The target groups for this priority setting are primarily researchers and research funding agents but may also include authorities and organisations which produce systematic reviews.

2 Background

2.1 Current state of knowledge

In December 2020, SBU published a report reviewing the scientific evidence of care for patients with long-term symptoms or sequelae (Long Covid) of the disease Covid-19. The limit for when a symptom is considered to be long-term was set at 6 weeks after onset of the disease. A summary was also made of studies showing which long-term symptoms occur in people with confirmed Covid-19-infection and how common these symptoms are. In addition to summarizing published studies, an inventory was made of studies currently in progress, registered in data bases of clinical studies [1]. The report identified several scientific articles about the pattern of symptoms and the proportion of patients afflicted. There were also a considerable number of studies in progress on this topic. With respect to treatment, only one published article and about 60 ongoing studies were identified as possibly relevant to this question. However, the subjects of these studies were mainly adult hospital inpatients. This led to the conclusion that further studies are needed into treatment of long-term symptoms of Covid-19. The report did not address other questions associated with long-term symptoms of Covid-19, such as possible causes or potential risk factors.

In conjunction with this commission, SBU decided further to audit and set priorities for research questions which, relevant stakeholders considered to be important. The reason for this initiative was primarily the awareness that SARS-COV-2 is a novel virus and that there is intensive research in this field, and it was therefore considered important to determine the perspectives of patients and professionals, as to which specific research questions they considered should be prioritised.

There are several different names for long-term symptoms of Covid-19. In this project we have adopted the definitions used in an earlier SBU-project on long-term symptoms of Covid-19, namely: the condition "Long-term symptoms of Covid-19" refers to all forms of long-term sickness, symptoms, complications and residual discomfort associated with Covid - 19. The definitions of long-term Covid-19 symptoms should, however, be regarded as preliminary and may change as knowledge of the condition increases. There is no formal definition but the condition itself goes by several names, some common terms are "Long COVID", "COVID-19 syndrome (PACS)" or, "post-acute sequelae of SARS-CoV-2 infection" (PASC) [2].

2.2 What is an evidence gap?

By scrutinizing and summarising research reports in a systematic review, it is possible to determine whether there is sufficient evidence to support different measures and methods, or whether more research is required, i.e., whether there are evidence gaps. Scientific evidence gaps may occur due to several reasons, for example there may be too few studies on the measure or method, or the available studies have a high risk of bias or show contradictory results. In such cases more primary research is needed to determine the advantages and disadvantages of the measure or method.

Since 2009, SBU, in accordance with the government directive, has been engaged in identifying and systematically compiling evidence gaps [3]. Evidence gaps identified by systematic reviews of the literature are summarised in SBU's database [4].

To close scientific evidence gaps through clinical research requires the cooperative effort of many different participants. The process may be likened to an ecosystem: for it to function, the separate activities are interdependent (Figure 2.1). The figure illustrates four essential, mutually dependent steps necessary to close evidence gaps in health and medical care, social services and services provided under LSS (Law regulating Support and Service to persons with certain functional disabilities), to ensure that the professions, consumers, and society in general derive maximum benefit from resources allocated to research. These steps involve systematic reviews, identification of scientific evidence gaps, priority setting of research questions and the financing and conduct of clinical research. At the centre of the wheel are those who can best identify questions which require both practice-based research and systematic reviews, namely users or patients, professionals, and relatives. They are also the key people when it comes to priority setting of research questions, participating in research design and implementation of the ensuing knowledge.

Figure 2.1
Evidence wheel.



2.3 Why do we need to set priorities for evidence gaps?

The purpose of this type of project is to highlight the perspectives of patients and clinicians in discussions as to which research questions should be given priority. In this context, the opinions of researchers, research funders and commercial agents are often more self-evident. However, it is also important to ascertain which research questions matter most to patients and clinicians i.e. topics considered highly relevant by the end-users. In an article from 2009, Chalmers och co-workers calculated that as much as 85 per cent of research funds awarded to practice-oriented research yields study results which are not applicable in practice for patients or healthcare personnel. A contributing factor is that questions which are important to these end-users are not given priority in research [5–7].

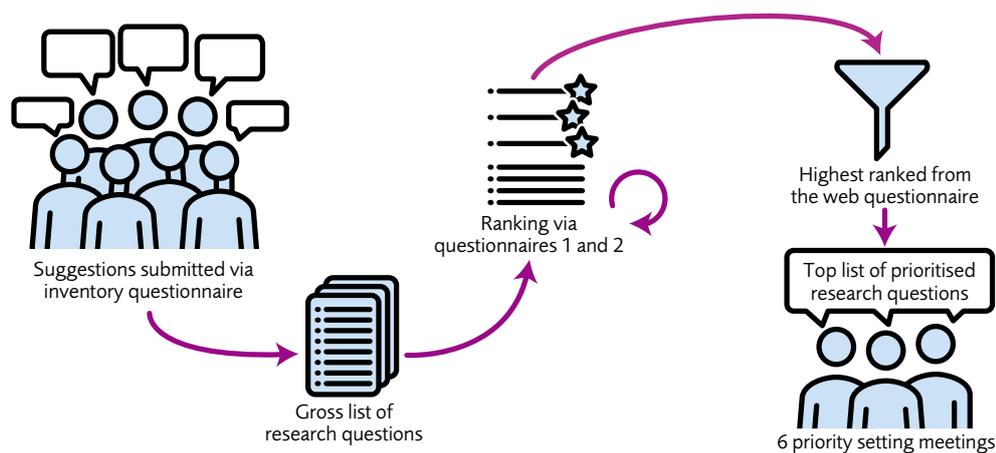
3 Method

The method applied in the project is derived from The James Lind Alliance. The method involves gathering and then prioritising research questions. A comprehensive view of the project design is presented in Figure 3.1. The study was conducted with the aid of the Delphi technique, whereby participants individually prioritise research questions in several sequential questionnaires. Between questionnaires, the results are categorised and presented to the participants, giving them the opportunity to change their submissions after seeing the other participants' opinions. The process concludes with a priority setting meeting of a smaller group of participants. This is usually in the form of a physical meeting for a full day, but because of the pandemic, digital priority setting meetings were used in the current project. To facilitate participation and allow space for discussion, we decided to have several briefer digital meetings instead of one longer meeting, because the digital format makes larger group discussions difficult.

The aim of having two questionnaires in this project was primarily:

- To present the results between the two priority setting questionnaires and give the participants the opportunity to re-evaluate their priorities
- To allow priority setting of the questions which were added to Questionnaire 1

Figure 3.1 Schematic illustration of the design of the project.



3.1 Project management team och working group

The project management team included SBU staff, a patient representative and one expert from the profession. The members of the project management team designed the questionnaires and information texts and analysed and summarized the results of the questionnaires and the priority setting meetings. No member of the project management team was involved in prioritising the research questions in the questionnaires or influenced the results of the priority setting meetings.

The working group comprises those people who declared their interest in participating in the project and who actively participated in the priority setting work, by responding to the two questionnaires. Some members of the working group also participated in the priority setting meetings.

A more detailed presentation of the project team, the external scrutineers and those who participated in the priority setting meetings is to be found in Chapter 6: Project group, external reviewers and the Scientific Advisory Committee.

3.2 Recruitment of participants to the working groups.

From 22nd September 2020 to 13th January 2021, there was an invitation on SBU's website, for expressions of interest in participating in the priority setting process. The information was also disseminated via SBU's social media, newsletters and through targeted emailing. Moreover, those who had declared an interest were asked to spread the information further via the information material which had been emailed to them on receiving their expression of interest.

The participants were required to give their name, email address and to indicate one of the following perspectives:

- I have/had long-term symptoms of Covid-19
- I am the relative of a person who has/had long-term symptoms of Covid-19
- I work clinically within the field
- I am a clinician or researcher and have my own experience of long-term symptoms of Covid-19, as a patient or the relative of a patient
- I am a researcher in this field (if you are active both clinically and as a researcher – choose this alternative)
- I have another relevant association to the disease, e.g. I work for a government authority, a region or another organization.

When Questionnaire 1 was issued, all the participants were asked if they would also like to participate in some of the priority setting meetings. Based on the response and the nominated perspective, an invitation was issued to a selection of these people, to create mixed groups for the different meetings. The aim was to create working groups comprising 4 to 6 participants per priority setting meeting, representing as many of the six perspectives as possible. In addition to perspective, selection was based on the following: gender, place of residence, and (for clinicians and researchers) profession.

The working group which prioritised the research questions comprised 553 people (Table 3.1).

Perspective	Declared interest	Responded to Questionnaire 1	Responded to Questionnaire 2	Participated in priority setting meeting
Total	553	418	410	29
Patient	415	321	309	9
Relative	25	18	17	5
Other	19	16	11	1
Clinicians	22	11	17	4
Clinicians (or researcher) and patient (or relative)	44	32	32	5
Researcher	28	20	24	4

Table 3.1
Participants and frequency of responses.

3.3 Inventory of research questions

An inventory of research questions was undertaken between 22nd September and 31st October 2020 by means of an open questionnaire on SBU's website [1]. Information about the questionnaire was disseminated on SBU's social platforms (Twitter, linkedIN and Facebook), through SBU's newsletter and via email to relevant interested parties [1].

In the questionnaire, SBU defined long-term symptoms as follows:

The term "Long-term symptoms of Covid-19" refers to all forms of long-term sickness, symptoms, complications and residual problems related to Covid-19."

All who participated in the questionnaire were required to nominate which perspective they considered themselves to represent, choosing from the following:

- I have /have had long-term symptoms of Covid-19
- I am a relative of a person who has/has had long-term symptoms of Covid-19
- I work clinically within the field
- I research within the field (if you are both clinically active and a researcher – choose this alternative)
- I have another relevant association with the disease, e.g., work for an authority, region, or other organization

The questionnaire also included information as to how a research question can be formulated and also whether the question applied to a certain part of the population or should be directed towards a specific outcome. Every participant was requested to choose ten important research questions. Each participant could however, if they wished, submit the questionnaire several times, which allowed a person to submit more than ten questions in all.

In total 508 people filled in at least one question each in the questionnaire. Most submitted more than one question. Most of the participants were people who themselves were afflicted, followed by clinicians and thereafter relatives [1].

3.4 Analysis and compilation of questions

The project group examined and analysed the research questions which had been proposed in the questionnaires. All responses received were extracted and a project manager at SBU read through all the incoming questions to classify the context. Questions which were not considered to refer to long-term symptoms of Covid-19 were excluded. In some cases, the texts received through the questionnaire were not formulated as questions: these were reformulated into questions by the project manager.

The project management team initially sorted the questions into different categories (for example, diagnosis, treatment etc.), and similar questions were then allotted to these main categories. The overarching main questions were written by the project management team and the questions received which were related to this heading were allocated accordingly. All the overarching headings are listed in Chapter 7.

For example, the following question was received: Are there alternative treatment methods, for example craniosacral therapy, acupuncture, acupressure, zone therapy and so on, which can ease the symptoms? This question was allocated to treatment/alternative medicine under the overarching heading: what are the positive and negative effects of alternative treatment methods? Later, other questions about alternative medicine were added under this heading, for example homeopathy preparations, quinine bark etc. A further example of combining questions may be seen in the following: What effect has cortisone inhalation? Is Alvesco more effective than other pharmaceutical inhalants? Does cortisone treatment have positive effects on long-term fever after Covid-19? Is there any association between rapid pulse and low oxygenation after mild exertion, before and after medication with cortisone? These questions were allocated to an overarching heading: What are the positive and negative effects of steroids/cortisone and other anti-inflammatory medications on people with long-term symptoms of Covid-19? The reason for grouping together and then sorting the questions is to allow and facilitate the subsequent setting of priorities, because a priority setting which contains too many unsorted research questions is considered too complicated. After the summary was completed, the project's expert advisers went through the questions to check for possible factual errors.

No literature search has been undertaken into published or ongoing studies relevant to questions about long-term symptoms of Covid-19, apart from those dealing with symptoms or treatment, compiled in December 2020 [1]. This means that there may by now be knowledge available about some of the questions which were submitted.

3.5 Prioritising research topics in the questionnaire

Everyone who had enrolled as a participant received two sequential questionnaires, published on the SBU website, to fill in. These questionnaires were designed using the online survey software Defgo [8]. In both questionnaires the participants were requested to prioritise the ten research questions they considered to be the most important. Before the questionnaires were issued, all participants received information about the aim of the project, which questions were included in the questionnaire and how they should fill in the questionnaires by email. In the first questionnaire, participants were also invited to suggest further research questions or suggest modification of the existing questions. The responses to the questionnaire were analysed in accordance with the following six perspectives and previously defined criteria as described in Table 3.2.

Based on information they provided when enrolling, the participants were grouped according to the following six perspectives.

- Patient
- Relative
- Clinicians
- Clinicians (or researcher) and also a patient (or relative)
- Researcher

Other (for example, representative of a professional association, an authority or user organization)

Table 3.2 Criteria for determining which questions should be carried forward.

Stage in process	Criteria	Comments
From Questionnaire 1 to Questionnaire 2	The 5 – 10 questions (apart from for example possibly newly introduced questions) which received the highest points per perspective were carried forward to Questionnaire 2, along with the 10 – 25 questions which were awarded the highest total number of points (the goal was to select about 50 questions or fewer for Questionnaire 2).	The 10 highest ranked questions per perspective and the ten with the highest total rank were carried forward.
From Questionnaire 2 to the priority setting meetings	The 5 questions awarded the highest points per perspective from Questionnaire 2, along with the 10 questions which were awarded the highest total points were carried forward (the aim was to have about 25 questions or fewer).	After carrying forward the five highest prioritised questions from each of the perspectives, we decided to expand the list by including the questions with the highest overall ranking, to achieve a total list of 25 questions.

Questionnaire 1 contained 97 research questions, 37 of which were carried forward to Questionnaire 2. Those carried forward were the ten which received most votes per perspective and in total.

In conjunction with the first questionnaire, several further research questions were proposed. Some were partly addressed by the existing questions, but several participants emphasised that they should be separate questions, so they were added. Examples of this are ID 102: What is the association between Postural Orthostatic Tachycardia Syndrome (POTS) and long-term symptoms of Covid-19? And ID 103: What is the relationship between hormones and long-term symptoms of Covid-19? For example, related to menopause, menstruation, metabolism. In all, the project team, after considering all the suggestions received, decided that nine of the suggested questions were new questions and these were added to the second questionnaire. Some wording in the major headings was also adjusted according to suggestions received. Thus, the second questionnaire comprised 46 questions in all, 37 retained from the first questionnaire and nine new questions.

Based on the result from Questionnaire 2, 25 research questions were carried forward to the consensus meetings.

3.6 Priority setting of questions at the final priority setting meeting

Before the meeting, those who were to participate in the priority setting meetings were requested to nominate their ten most important research questions once again, but this time to rank them from 1 to 10 and reflect on the motivation for their priorities. Before the meeting, information was sent out to the participants about the agenda, the structure of the meeting and the remaining research questions.

SBU's role in the priority setting meetings was to organize and facilitate the discussions, and to ensure that the prioritising was achieved by mutual participation of all the participants and that everyone had the opportunity to be heard. However, SBU staff did not actively participate in the discussions and did not direct which questions the participants prioritised.

At the meeting, the moderator (from SBU) first presented the form of the discussion. Then each participant briefly presented his or her priority list and their underlying motivation. Finally, a discussion was held with the full working group, wherein the participants reasoned their way to a final, mutually agreed top list. During the discussion, digital cards describing the research questions were used: the moderator moved these cards to the desired place in the ranking, according to the participants' preferences.

The participants in the priority setting groups were given the opportunity to combine questions which they considered to be very similar. If any group did this, they were requested to state, if possible, which of these questions they considered most important. This procedure provided information as to which questions were considered similar and was also applied during the summing up, when the project management team took note of whether a question had been

selected as a secondary question by one or more of the groups. However, the working groups were not given the opportunity to change the wording of the questions, because this would have necessitated discussion involving the entire group, to ensure that all were in agreement about the change. An exception was made with respect to ID69, which addressed risks of vaccination in those with long-term symptoms of Covid-19. After the initial priority setting meeting, this question was changed to "effect of vaccination". In this case the initial priority setting group highlighted the importance of research investigating the overall effect, i.e., possible positive effects as well as possibly negative effects. The change was discussed in all the priority setting groups, and all groups considered that this new wording was preferable.

The results of the six different meetings were then combined by the project team, based on the criteria described below. All participants in the working groups had been informed about this procedure at the beginning of the priority setting meetings.

Criteria for combining the results of the various meetings.

The results of the various workshops were combined as follows:

Questions ranked as most important were awarded 10 points and a question ranked in tenth place was awarded 1 point. The remaining questions were awarded points in descending order in between the highest and lowest ranked questions.

Place	1	2	3	4	5	6	7	8	9	10
Point	10	9	8	7	6	5	4	3	2	1

If several questions had the same ranking, then the common points for these placements were shared among them.

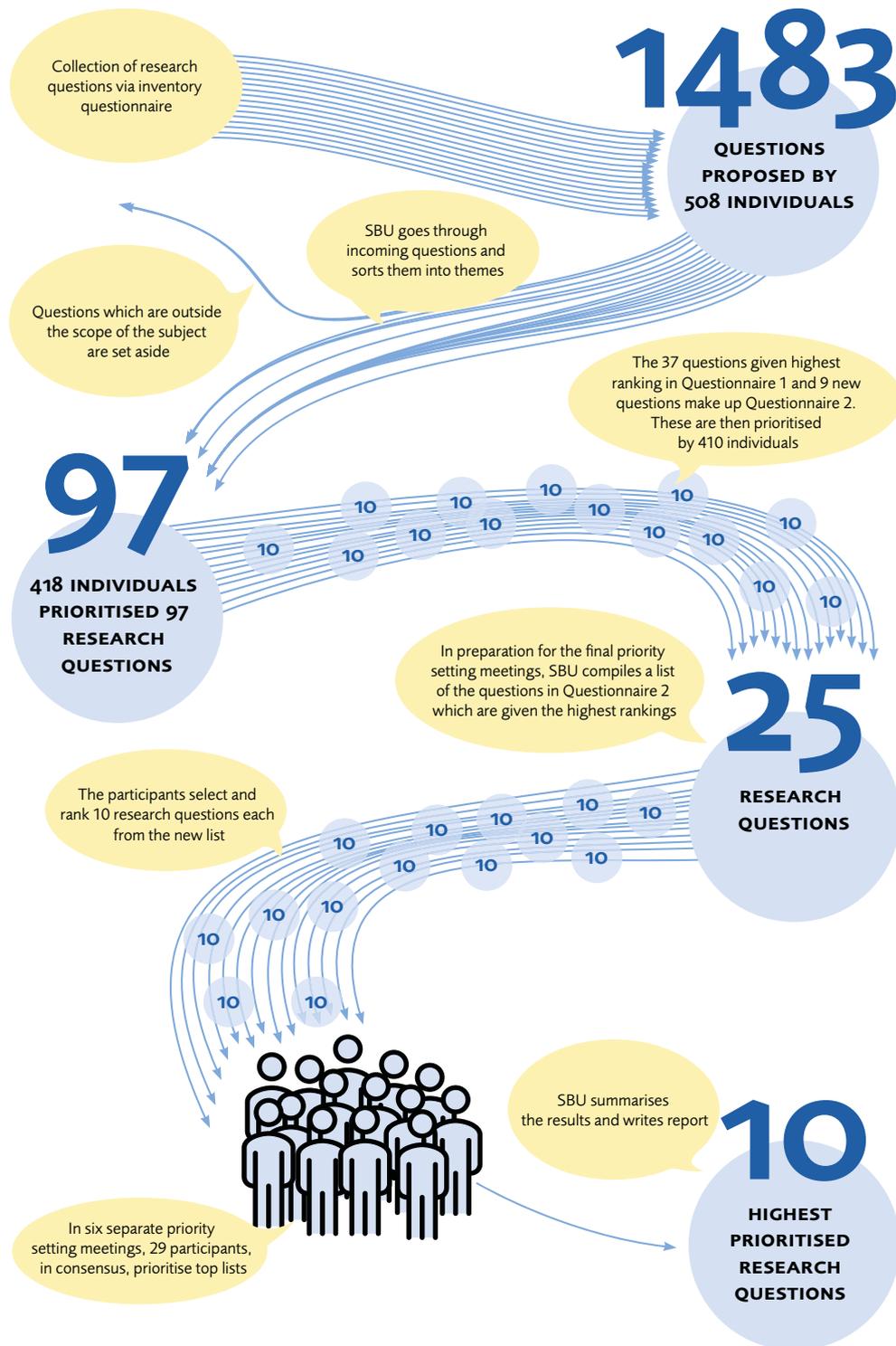
After the priority setting meetings the final top ten list was sent to all participants in the working groups, and they were invited to comment.

4 Results

The audit questionnaire yielded in total 1483 research questions, proposed by 508 individuals [1]. After excluding questions which were beyond the scope of the subject and combining questions on a similar theme, the result was a list of 97 comprehensive questions. Chapter 7 highlights all the comprehensive research questions and indicates which were carried forward to the second questionnaire, and those which were then carried forward further to the priority setting meetings.

In all 553 people expressed their interest in participating in the working groups. Of these, 418 (76%) answered Questionnaire 1 and 410 answered Questionnaire 2 (74%). From Questionnaire 1, the 37 highest ranked research questions and nine new questions were carried forward to Questionnaire 2. After analysis of Questionnaire 2, there remained 25 questions which were carried forward to the digital priority setting meetings. The priority setting process is described in Figure 4.1. The results of the two questionnaires are presented in Appendix 1

Figure 4.1 Flow chart of the project process.



4.1 The top ten research questions about long-term symptoms of Covid-19, ranked by priority

After discussion of the research questions in the six priority setting meetings, the participants at each meeting decided on a top ten list.

Subsequently a final top list was compiled from these meetings (Table 4.1). The results from the six groups were combined by awarding points to the research questions, corresponding to their ranking, and the points were then summed up. This resulted in some of the questions being awarded the same number of points: these share an equal place in the top list.

The ranking in the top list does not necessarily reflect the order in which research should be conducted, but merely lists the questions which it is considered important to address. As some of the questions are broad, several research studies may be necessary to address them. Some of the research questions may be interdependent and, in such cases, there may be an advantage in designing future studies which cover a combination of questions.

The priority setting covers a broad area of a very active field of research. It is therefore important that researchers consider established collective knowledge before they begin research, even on these prioritised questions. It is also important that published studies are compiled and are systematically reviewed in future.

Top 10 list of prioritised research questions about long-term symptoms of Covid-19 (1 = highest ranking).

1	What treatment is effective against persistent neurological symptoms and cognitive disturbances (such as brain fog, memory loss, difficulty concentrating, fatigue, numbness, tremor, headache) associated with Covid-19? How can rehabilitation efforts after long-term symptoms of Covid-19 be optimised and what measures should be included (occupational therapy, physiotherapy, psychology, social worker, speech therapist, dietitian etc.)?
3	What is the most effective treatment for long-term impaired breathing function/ oxygen uptake or problems with respiratory arrest, associated with Covid-19?
4	Why do certain people develop long-term symptoms of Covid-19?
5	How can an objective diagnosis be made of people with long-term symptoms of covid-19, regardless of whether they have had a positive PCR test during the acute phase, or if they have demonstrable antibodies?
6	Can expanded diagnosis, to investigate which organs are involved, result in better treatment and eventually prevent future complications in people with long-term symptoms of Covid-19?
7	What is the underlying cause of the various patterns of symptoms in people with long-term symptoms of covid-19?
8	What treatment can be given during the acute phase to prevent the development of long-term symptoms of Covid-19? What clinical manifestations occur in persons affected by long-term symptoms of Covid-19?
10	Is the immune response (e.g. T-cell response, antibodies to Covid-19, development of autoimmunity) different in people with long-term symptoms of Covid-19?

Table 4.1 Top 10 list.

4.1.1 Motivation and reasoning in support of the priority setting

What treatment is effective against persistent neurological symptoms and cognitive disturbances (such as brain fog, memory loss, difficulty concentrating, fatigue, numbness, tremor, headache) associated with Covid-19?

Among the arguments in support of research into treatment were for example, the fact that many people are afflicted and currently undergoing various types of treatment, but that this is not being done in a structured way, and it is therefore not possible to draw conclusions from this treatment. It was also pointed out, mainly by the patient and relative groups, that even if it is useful to have answers as to the cause and frequency of the symptoms, it is also necessary to conduct treatment studies, to generate knowledge about the effect of various types of treatment, to facilitate recuperation of those currently afflicted by long-term symptoms.

The group discussed the fact that little is generally known about treatment of such symptoms and it therefore seems more difficult to proceed based on knowledge available from other conditions. The discussion also considered the fact that these symptoms can be more difficult to measure and that the health status of people with such symptoms is not taken as seriously by clinicians as the status of those whose symptoms are easier to measure. The patients pointed out that these symptoms had a pronounced negative impact on quality of life and that research about treatment is therefore important. Several of the groups also discussed the fact that these patients often received rehabilitation and this question was to some degree related to the question of how rehabilitation measures can be optimized. However, the groups considered that treatment could comprise more than rehabilitation and that the question of rehabilitation was also of great importance in relation to other symptoms and can differ between hospital inpatient care/ ICU care and home care. The questions were therefore prioritized individually.

1. How can rehabilitation efforts after long-term symptoms of Covid-19 be optimised and what measures should be included (occupational therapy, physiotherapy, psychology, social worker, speech therapist, dietitian etc.)?

During the meetings it was agreed that more knowledge about this topic was very important for a large group of patients, not only those who had been treated in hospital and in intensive care, but also for those cared for at home. It is important to know which rehabilitation measures effective, what competencies are required in the rehabilitation team and how the teams can be organized to achieve the best effect. Several groups gave this question priority over the question of what type of rehabilitation best facilitated return to work, as they considered that this question included a wider range of afflicted individuals (such as children, pensioners, students, the unemployed, etc.)

3. What is the most effective treatment for long-term impaired breathing function/ oxygen uptake or problems with respiratory arrest, associated with Covid-19?

Several groups pointed out that the question overlaps that on cardiopulmonary symptoms and that to some extent some of the research also overlaps. It was therefore considered that research into this question should be able to generate further knowledge about treatment which affects the cardiovascular system. When selecting from the various questions, it was decided that research into treatment of breathing capacity was more important. This question also covers research into treatment of subjective symptoms which patients describe, but for which there are no objective signs.

4. Why do certain people develop long-term symptoms of Covid-19?

There is considerable knowledge about risk factors related to acute Covid-19 and death, but there is inadequate reliable knowledge as to whether certain factors create an increased risk of developing long-term symptoms of Covid-19. More research should yield further knowledge as to why certain people are afflicted and whether the risk varies according to - for example, - age, gender, occupation, blood group, genetic factors, hormonal factors, immunological factors, or other factors. This knowledge was considered important, as the foundation of future research into preventive measures and expanding our knowledge of the mechanisms underlying various symptoms and causes, hence improving the potential for future treatment.

5. How can an objective diagnosis be made of people with long-term symptoms of covid-19, regardless of whether they have had a positive PCR test during the acute phase, or if they have demonstrable antibodies?

This research topic explores means of objectively confirming that a patient has symptoms due to a previous Covid-19 infection. This question was highlighted for several reasons: participants with a healthcare perspective considered that it was important to ascertain that those receiving treatment have had Covid-19, excluding another underlying reason for the symptoms: this can influence prioritising of patients during periods of high demand for hospital care. Patients, and particularly representatives for the Swedish Covid-19 Association, pointed out that people who have neither a positive PCR nor a positive antibody test are not as well received by clinicians and find it harder to be taken seriously when describing their symptoms: instead, they can be diagnosed with anxiety or other psychiatric conditions without a thorough investigation. This is also important for future research, to ensure that research is conducted on subjects with confirmed long-term symptoms of Covid-19 and not symptoms of other origin, as this can influence the results of the studies.

6. Can expanded diagnosis, to investigate which organs are involved, result in better treatment and eventually prevent future complications in people with long-term symptoms of Covid-19?

The other question concerns which examinations should be undertaken to detect organ changes which may be the cause of the patient's symptoms, but which may not be disclosed by traditional methods of examination. For example, people with a healthcare perspective pointed out that traditional x-rays are inadequate for disclosing the changes which occur in the lungs. The groups emphasised the need for diagnostic methods which were able to give a more reliable diagnosis, for example blood gas tests, measurement of oxygen saturation while walking, magnetic resonance cameras and xenon gas. It was also pointed out that improved knowledge in this area would facilitate more consistent diagnostic and investigative procedures throughout Sweden, and this should not depend on which speciality one "happened" to be allotted to. Some groups pointed out that now there can be great variations in diagnosis and access to treatment, depending on where you live and the regional policy on diagnosis. This applies in particular to those who did not have a positive PCR/antibody test. It was pointed out that even if there is an attempt to comply with WHO's recommendations, there is a risk that these people will be given lower priority at times of high demand for inpatient care.

7. What is the underlying cause of the various patterns of symptoms in people with long-term symptoms of covid-19?

The question reflects the physical conditions that give rise to specific symptoms. For example, the cause of increased heart rate, brain fatigue, prolonged fever, dizziness, or other symptoms that can occur.

Some participants reasoned that this question should also include investigation as to what extent it is the virus, or the patient's own immune response which is responsible for the various symptoms.

8. What treatment can be given during the acute phase to prevent the development of long-term symptoms of Covid-19?

Many of the participants considered it important to investigate measures which could be taken during the acute phase of the infection to prevent long-term symptoms. Some participants reasoned that current ongoing treatment studies on people in the acute phase might to some extent provide answers to this question, provided the studies have an adequate follow-up period. Moreover, it should be possible to compare treatment during the first and second waves respectively, which differed somewhat, and compare the occurrence of long-term symptoms. There is a risk that these studies focus more on seriously ill patients and several groups emphasised the importance of also studying possible preventive measures for those who are not as acutely ill and are being cared for at home.

8. What clinical manifestations occur in persons affected by long-term symptoms of Covid-19?

The objective clinical manifestations and organ changes occurring were a fundamental question. Many groups chose to combine this question with that on symptoms which arise and how long the symptoms last, reasoning that research studies investigating underlying organ changes and clinical manifestations would also probably collect information regarding the patients, self-reported symptoms. Here there was a wish for research which included a long follow-up period, to disclose how long the changes persisted and whether there was a risk that they would become chronic. This question was related somewhat to the question about expanded diagnosis, because certain clinical findings/organ changes might require special diagnostic equipment to be identified.

10. Is the immune response (e.g. T-cell response, antibodies to Covid-19, development of autoimmunity) different in people with long-term symptoms of Covid-19?

The final question in the top list concerns the role of the immune system and how it differs in people who develop long-term symptoms and whether this can explain why certain people are afflicted. The participants hope that knowledge about this topic will be able to give some answers to the question of the effect of vaccination in people with long-term symptoms.

4.1.2 Non-prioritised questions

There were questions not included in the final top list, which were discussed and prioritised by one or several groups, but not the majority of the groups. Some questions were not ranked high enough to be included in the final top list. The reasoning about some of these questions is presented here.

All the groups considered that the question about the vaccine's effect on people with long-term symptoms was very important. The groups which decided not to prioritise this question believed that research was probably in progress and given the rapid rate of vaccination globally, an answer to the question would soon emerge. They also reasoned that the question would eventually be answered in part by research into the immune response, which was prioritised in tenth place.

Another question which was the subject of lively discussion in all the meetings was how care should best be organised for these patients. All the groups were agreed that this was an extremely important issue and that there was great potential for improvement. However, opinions differed as to whether research was needed on this question, or whether it was more of a political issue. Those who opted to prioritise the question considered that there was a need for support, based on research, to achieve organisational changes. Many groups also pointed out that this question is relevant not only for just this patient category but is considerably broader.

With respect to How the Swedish Social Insurance Agency's regulations and decisions affect recovery and rehabilitation of patients with long-term symptoms of Covid-19, all groups considered that this should be emphasised in the report, even it was not prioritised as a research question. The groups were unanimous in regarding this question as very important, but as with the organisation of healthcare, this is more of a political issue. The groups reasoned that this question is also much broader and in fact concerns many more patient categories than those with long-term symptoms of Covid-19. Possible research should therefore include an investigation into how the National Health and Medical Insurance Scheme regulations affect all persons with sick leave on a long-term basis, regardless of the underlying illness.

Several groups emphasised research into positive and negative effects of steroids/cortisone and other anti-inflammatory or analgesic medication as important. This treatment is used today for patients with long-term symptoms of Covid-19, and there is also pressure from patients to be given this treatment. It is therefore important to determine the effects of this treatment: this could be achieved by means of a randomised controlled study (RCT). Several groups however, pointed out that this question could be included in the other questions about treatment. Certain groups considered that this question would be answered anyway and did not need to be included as a prioritised question.

Feedback from participants in the working groups (in all, 20 comments were received by email).

All comments were predominantly positive about the project and the top list. The comments were either very brief: the respondent thanked us for the information and stated that they had found participation a positive experience, while some included a little more reasoning about what they considered researchers should concentrate on, within the framework of the questions in the top list. Moreover, some suggested that future research studies should address more than one of the questions in the top list. There were also comments about the wording, i.e., how the questions were formulated. The only question mentioned in the comments received which was not in the top list was the question of the effect of a vaccine on people with long-term symptoms of Covid-19.

5 Discussion

There is often a gap between research being conducted and knowledge and improvement requested by patients and clinicians [6,7,9]. In this project, participants with personal, clinical or research experience of long-term symptoms of Covid-19 were invited to prioritise specific research questions which they together consider to be most important: that there is currently insufficient knowledge about these topics. The aim is to highlight research questions which matter most to those who will be directly impacted by new research results.

Although most of the participants were people who had themselves been afflicted with long-term symptoms of Covid-19 infection, the responses to the questionnaire have been weighted to ensure that every perspective has been given equal opportunity to influence the results. Moreover, those who participated in the closing priority setting meetings were selected so that there would be equitable involvement of those with a patient/relative perspective and those with healthcare/research perspectives

Linking the results to other priority listings of research questions about Covid-19

SBU has not undertaken a systematic search to identify other possible priority settings of research questions about long-term symptoms of Covid-19. There are, however, articles and reports which address the issue of the need for research in this population. An article published in September 2020 addressed the need for research in this population [10] and NIHR addresses the research need in its report "Living with Covid19" [11]. Another recent publication is Research priorities for Long Covid: refined through an international multi-stakeholder forum [12]. In general, it may be stated that these reports do not follow the same method as the present project, i.e. an audit of research to date,

followed by priority setting of research questions. The prioritising in the published reports is also somewhat broader, in terms of the wording of the research questions, than in the present project. There are, however, certain similarities: in general, the emphasis is on the importance of understanding the symptoms and the course of the illness, and the underlying causes and treatment.

Strengths and weaknesses A possible weakness in the project design could be that important research questions were completely overlooked during the auditing procedures. That this was probably not the case is indicated by the fact that the material was considered to be saturated and most of the questions, with minor variations, appeared many times. As more knowledge is disclosed and new research questions are constantly being proposed for this relatively new disease, the participants were also invited to suggest new questions in the initial questionnaire. Compilation of the research questions is dependent on the wording of the questions submitted and how many questions were very similar. If many suggestions were received about the same specific topic, this was adopted as a separate, comprehensive question. This means that some questions are more specific than others and different research methods may be required to answer them.

The design of the project, based on an open expression of interest in participating, means that selection is not random: there can be bias as to which people choose to apply and participate in projects such as these. To circumvent this risk of selective participation, information about the project was disseminated both by information to patient and professional associations and via social media and newsletters. The project managers considered that information about the project was well-disseminated and interest in participating was strong. However, there is always a risk that such information does not reach certain sections of the population and that their questions and perspectives are overlooked, for example: people of foreign background, people with a disability, the elderly and children and young people.

Most of those who expressed an interest in participating were people with personal experience of the disease. Clinicians comprised the smallest group. We can only speculate as to why there were fewer expressions of interest among health workers: one reason may be that health workers have to date had limited contact with patients experiencing long-term symptoms of Covid-19, unless they have themselves been afflicted or are conducting research in the field. It is also possible that because at present, certain parts of the health services are under great strain, staff lack the time, energy or desire to participate. Moreover, because the pandemic is still active, staff may consider that to date they have not acquired a professional perspective of the field and the concept of long-term symptoms of Covid-19 is to date not fully established.

All participants in the working groups had the opportunity to express their interest in participating in the priority setting groups. Selection thereafter was based on an attempt to form groups of 4 – 6 at every meeting, with as even a distribution as possible between people with patient/relative perspectives and those with healthcare/professional perspectives. However, none of the working groups can be considered to cover all the perspectives and it may be argued

that including other participants in the group could have yielded a different result. The strengths of the compilation of the working groups are that the participants came from different regions of the country, were of varying age and gender, and different professions, and represent both afflicted people with persistent symptoms, people who have recovered over time, those who were cared for in hospital or at home, and representatives of various professions, such as registered nurses, medical doctors with different specialties, enrolled nurses, speech therapists, physiotherapists and occupational therapists and psychotherapists.

A methodological difference between the present project and projects usually conducted by The James Lind Alliance is that throughout the process we have included researchers as one perspective. This perspective is not usually included in the final stages of the priority setting process because active researchers can be considered to have conflicts of interest. We chose to make an exception to this, because Covid-19 is a novel disease and research into the long-term symptoms is at an initial phase. Another reason for inclusion of researchers is that many people who are researching these topics are also those who have had most contact with these patients in the hospital setting. Moreover, we considered it important because the framework of the project did not allow a thorough search of all the available research: thus the researchers who were participating in the project could provide information in cases where further knowledge was required about the research questions being given priority. To reduce possible dominance of opinion, the project group ascertained that the researchers who participated in the priority setting meetings represented different disciplines and that discussion about their own fields of interest did not dominate during the meetings. It is also possible that nursing personnel, patients and relatives have conflicts of interest, and therefore every potential participant in the priority setting meetings was required to declare possible conflicts of interest before being included.

The frequency of responses to both questionnaires was relatively high, 76 and 74 per cent respectively. There is, however, a risk that the volume of information to be read and understood can have been overwhelming for certain people who are still suffering from severely impaired function. We have however, seen no difference in attrition among representatives for the various perspectives. To counteract this, we have tried to keep the information brief and easy to read and suggested that participants are welcome to seek help of a relative or the like when completing the questionnaire. In sending out the second questionnaire, we also decided to include all who initially notified their interest in participating, even if they had not responded to Questionnaire 1. Our hope was that those who may have had problems prioritising among the initial 97 questions, might be able to participate by prioritising from the shorter list in the second questionnaire.

Usually, projects of this kind are concluded with a physical full day meeting, of about 12 to 18 participants. Because of the restrictions at the time for a meeting of this size, the meeting was held digitally instead of in person. Other modifications made for the final priority setting meeting were to hold several shorter meetings instead of one longer meeting. Other modifications were also

made to the meeting structure to ease participation, as even a digital meeting of less than three hours can be difficult for participants, especially for those with cognitive issues, but also for clinicians with heavy workloads. Partakers were offered the opportunity to participate for a limited time or the opportunity to present their priority list early in the meeting. The advantages of this plan are: people who suffer, for example, from fatigue and cognitive dysfunction have a greater opportunity to participate; we could offer a larger group the opportunity to participate and so include more perspectives; and participants were given a choice of several meeting dates, which improved the potential for people to participate. The project group decided that a concluding discussion with all participants was not feasible, not only for practical reasons (like finding a time when everyone could attend) but also because of the limitations of the digital format (difficult to hold group discussions with a larger number of participants). We have therefore based the final results on a combination of the top lists compiled at each of the six priority setting meetings. However, to consolidate the results, the top list was sent out to all participants for perusal and comments. The disadvantage of this procedure is that we had no final mutual concluding discussion involving all the participants. Such a discussion could have resulted in a change in ranking of some of the questions, or inclusion of a question which was just outside the list, and in turn, removal of one of the existing questions. However, it is the opinion of the project team, based on the feedback we received, that the majority of participants are satisfied with this top list.

It may be stated that in general, there were similar discussions in all six priority setting meetings. All emphasised the importance of multifaceted research, covering the pattern of symptoms, cause, diagnosis, and treatment. It was acknowledged that as a basis for future research into treatment, it was important to establish the cause and the pattern of symptoms and to research the immune response, but it was also emphasised that initiation of treatment studies is important for those who currently have long-term symptoms. The groups pointed out that the types of treatment given this population vary, and that at present they are given inconsistent information about what rehabilitation etc. they should consider. Therefore, there was emphasis on the importance of a structured approach, through clinical research, to determine the effects of various forms of treatment. In this context the importance of study design was also discussed. Unfortunately, SBU's experience from previous systematic reviews is that in a large proportion of studies, the study design yields result that cannot be implemented. For example, uncontrolled studies, small studies, or studies in which the population and/or the intervention are inadequately described to allow replication of the study, or inclusion of the results in a systematic review and clinical application.

Covid-19 is a novel disease, and it may be debatable whether at this early stage it is an advantage or a disadvantage to compile a priority list of research questions. With high research activity, information on prioritised questions might enhance the potential for research to provide answers to those questions nominated as important by patients and health workers. At the same time the knowledge base is rapidly changing because of the intensive research activity and this could influence the results of the priority setting, and its useful life.

With respect to the research questions listed as priorities, a thorough audit of the state of research has not been undertaken. In December 2020, SBU published a report on research about the incidence of symptoms and treatment for people with long-term symptoms of Covid-19. However, this field of research is so dynamic that there may already be several new studies which influence the state of knowledge in the field. This implies that there are probably both published and ongoing studies in several of the prioritised research fields. It is therefore important that before initiating a new study, researchers update their assessment of the current state of knowledge. It is also important that in future, studies, after publication, are collated and evaluated in systematic reviews.

6 Project group

6.1 Experts

JUDITH BRUCHFELD
Senior medical officer,
Karolinska University Hospital

EMMA MÅRTENSSON
Patient advocate

6.2 Secretariat

MARIE ÖSTERBERG
Project Manager

IRINI ÅBERG
Project Administrator

CHRISTEL HELLBERG
Project Manager

SOFIA TRANÆUS
Head of department

6.3 Working group for priority setting meetings

Table 6.1 Working group for priority setting meetings

Name	Perspective	Occupation/ other additional perspective	Participated in priority setting meetings
Maria Rydberg	Personal experience of long-term symptoms of Covid-19		1
Anonymous	Relative		1
Mia Marttinens	personal experience of long-term symptoms of Covid 19/relative	Midwife	1
David Gyll	Clinician (General medicine practitioner)		1
Marta Santander	Personal experience of long-term symptoms of Covid-19		2
Lars Nord	Personal experience of long-term symptoms of Covid 19		2
Maziar Mohaddes	Other (Scientific secretary of Swedish Orthopaedic Association)	Orthopaedic surgeon, Researcher (Associate professor, Orthopaedics), Chief Medical Officer	2
Sture Eriksson	Researcher (Associate Professor, Psychogeriatric medicine)	ME relative.	2
Stefan Berg	Personal experience of long-term symptoms of Covid 19		3
Mathilda Sundvall	Personal experience of long-term symptoms of Covid-19	Representative of Swedish Covid Association	3
Gisela Rosenkvist	Relative	Registered nurse	3
Lotti Orwelius	Researcher (Intensive care)	Intensive care nurse	3
Cia Skog	Personal experience of long-term symptoms of Covid 19	Psychotherapist	3
Catarina Trägert	Personal experience of long-term symptoms of Covid- 19	Paediatrician, Representative of Swedish Covid Association	3
Inger Nordlander	Relative		4
Lasse Hagman	Personal experience of long-term symptoms of Covid-19		4
Hanna C Persson	Researcher (Rehabilitation medicine)	Senior physiotherapist	4

The table continues on the next page

Table 6.1 continued

Name	Perspective	Occupation/ other additional perspective	Participated in priority setting meetings
Lisbeth Friman	Personal experience of long-term symptoms of Covid -19	Registered nurse, Political expert, Greater Stockholm region	4
Ted Eriksson	Relative		5
Malin Sylveston	Personal experience of long-term symptoms of Covid -19		5
Artur Fedorowski	Clinician (cardiology)	Researcher (Associate professor, Cardiovascular Research), Senior Medical Officer	5
Annica Lifbom Johansson	Clinician (Registered physiotherapist)		5
Eva Höglund	Personal experience of long-term symptoms of Covid-19/relative	Specialist registered nurse	5
Liisa Pettersson	Relative	Physiotherapist	6
Sara Johansson	Personal experience of long-term symptoms of Covid-19		6
Kristina Franzon	Personal experience of long-term symptoms of Covid-19	Speech therapist	6
Kristian Borg	Researcher (Professor, Rehabilitation medicine)	Chief Medical Officer	6
Pia Nyberg	Personal experience of long-term symptoms of Covid-19	Enrolled Nurse	6
Katarina Niward	Researcher (Inflammation and infection)	Chief Medical Officer infectious disease	6

6.4 External reviewers

LARS-MAGNUS ANDERSSON

MD, PhD, Chairman Infectious diseases Clinic, Chief Medical Officer, Associate Professor Sahlgrenska University Hospital/East, Chairman of the Swedish Association of Specialists in Infectious Diseases.

MATS ULFENDAHL

Director of Research, Region Östergötland.

SBU appoints external scrutineers to evaluate its reports. They have contributed valuable comments which have improved the report. SBU has however, not always been able to accommodate their proposals for change and the external scrutineers do not necessarily support all the conclusions and texts in the report.

6.5 Conflicts of interest

In accordance with SBU's requirements, the experts, external reviewers participating and all participants in the priority setting meetings in this project have submitted statements about conflicts of interest. These documents are available at SBU's secretariat. SBU has determined that the conditions described in the submissions are compatible with SBU's requirements for objectivity and impartiality

6.6 SBU's scientific advisory board

SVANTE TWETMAN

Chair (dental), Professor emeritus,
University of Copenhagen

CHRISTEL BAHTSEVANI

Malmö University, vice chair
(care science)

ANNA EHRENBORG, FALUN

Dalarna University (care science)

ANNA SARKADI

Uppsala University (social medicine)

ATA GHADERI, UPPSALA

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MARTIN BERGSTRÖM

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PERNILLA ÅSENLÖF

Uppsala University (physiotherapy)

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Stockholm University (social care)

SVERKER SVENSJÖ

Falun and Uppsala University
(medicine)

ULRIK KIHLMAN

Uppsala University (ethics)

7 Tables of questions received

ID nr	Category	Research question	Question prioritised
1	Symptom	Are there differences in the course of the disease and types of persistent symptoms of Covid-19 between: men and women, people from different age groups, or people of different socioeconomic status (education, income, non-European origin)?	Carried forward to Questionnaire 2, then to priority setting meeting
2	Symptom	How do long-term symptoms of Covid-19 affect the body in people with other underlying health conditions?	
3	Symptom	How long can various symptoms of Covid-19 persist and do the different symptoms follow a specific course?	Carried forward to Questionnaire 2, then further to priority setting meeting
4	Symptom	How do the type and duration of long-term symptoms of Covid-19 and functional incapacity differ between those who needed intensive care and those who managed with self-care at home?	Carried forward to Questionnaire 2
5	Symptom	What different kinds of long-term symptoms of Covid-19 occur and what proportion of patients are afflicted by the various symptoms?	Carried forward to Questionnaire 2, then further to priority setting meeting
6	Symptom	Is there a risk that certain long-term symptoms/ complications of Covid-19 can become chronic?	Carried forward to Questionnaire 2 and then on to priority setting meeting

Tabell 7.1 Tables of questions received. Questions added after the first questionnaire are listed as ID number 100 to 108.

The table continues on the next page

Table 7.1 continued

ID nr	Category	Research question	Question prioritised
7	Symptom	What clinical manifestations occur in persons affected by long-term symptoms of Covid-19?	Carried forward to Questionnaire 2 and then on to priority setting meeting. Included in final top list
8	Symptom	Which psychological symptoms occur in persons with long-term symptoms of Covid-19?	
9	Symptom	Which of the long-term symptoms of Covid-19 are potentially serious and which can confidently be allowed to heal themselves?	Carried forward to Questionnaire 2 and then on to priority setting meeting
10	Symptom	Which long-term symptoms of Covid-19 have the greatest effect on the daily life of patients?	Carried forward to Questionnaire 2
11	Treatment/ complementary and alternative medicine	What are the positive and negative effects of complementary and alternative treatment methods for people with long-term symptoms of Covid-19?	
12	Treatment/ pharmaceuticals	What are the positive and negative effects of using immunosuppressive drugs in patients with long-term symptoms of covid-19?	
13	Treatment/ pharmaceuticals	What are the effects of treatment with antiallergenic drugs for people with long-term symptoms of Covid-19?	
14	Treatment/ pharmaceuticals	What are the positive and negative effects of betablockers on people with long-term symptoms of Covid-19?	
15	Treatment/ pharmaceuticals	What are the positive and negative effects of steroids/cortisone and other anti-inflammatory or analgesic drugs on people with long-term symptoms of covid-19?	Carried forward to Questionnaire 2 and then on to priority setting meeting
16	Treatment/ pharmaceuticals	What effects do antibiotics have on people with long-term symptoms of Covid-19?	
17	Treatment/ pharmaceuticals	What are the effects of antiviral treatment on people with long-term symptoms of covid-19?	
18	Treatment/ pharmaceuticals	What effects do immunomodulatory drugs have on people with long-term symptoms of Covid-19?	
19	Treatment/ pharmaceuticals	What effects do bronchodilators have on people with long-term symptoms of Covid-19?	
20	Treatment/ pharmaceuticals	Can the long-term symptoms of Covid-19 be exacerbated by use of certain medication intended for other conditions?	
21	Treatment/ pharmaceuticals	What is the effect of anticoagulants on people with long-term symptoms of Covid-19?	
22	Treatment/ pharmaceuticals	What are the effects of ataractic (anti-anxiety) and antidepressant medicine on people with long-term symptoms of covid-19?	

The table continues on the next page

Table 7.1 continued

ID nr	Category	Research question	Question prioritised
23	Treatment/ pharmaceuticals	What effects are there, on the course of Covid-19 and on the body, from long-term treatment with analgesics?	
24	Treatment/ psychological treatment/ support	What effect does psychological/ psychiatric treatment have on people with long-term symptoms of Covid-19?	
25	Treatment/ psychological treatment/ support	What is the effect of various forms of support for relatives of people with long-term symptoms of Covid-19?	
26	Treatment/ psychological treatment/ support	What type of support can people with long-term symptoms of Covid-19 need and can this hasten recovery?	Carried forward to Questionnaire 2
27	Treatment/ rehabilitation	Do people with long-term symptoms of Covid-19, who have not required hospitalisation, need the same type of rehabilitation as people who have been hospitalised?	Carried forward to Questionnaire 2
28	Treatment/ rehabilitation	How can rehabilitation efforts after long-term symptoms of Covid-19 be optimised and what measures should be included (occupational therapy, physiotherapy, psychology, social worker, speech therapist, dietitian etc.)?	Carried forward to questionnaire 2, then to priority setting meeting, then on to the top priority list
29	Treatment/ rehabilitation	What physiotherapy treatment has the best effect on people with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2
30	Treatment/ rehabilitation	What interventions should occupational therapists offer people with long-term symptoms of Covid-19?	
31	Treatment/ rehabilitation	What is the effect of cognitive training on people with long-term symptoms of Covid-19?	
32	Treatment/ rehabilitation	What rehabilitation/measures are optimal to facilitate return to work for people with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2, then further to priority setting meeting
33	Treatment / rehabilitation	What is the effect of graded exercise training on people with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2
34	Treatment / rehabilitation	Does pacing work for people with long-term symptoms of Covid-19?	
35	Treatment/ symptoms	What is effective treatment for people with long-term symptoms of Covid-19 experiencing disturbed sleep?	
36	Treatment/ symptoms	How can the cyclical course of symptoms best be reduced in cases of long-term symptoms of Covid-19?	
37	Treatment/ symptoms	What treatment is effective against long-term loss of sense of taste and smell associated with Covid-19?	Carried forward to Questionnaire 2

The table continues on the next page

Table 7.1 continued

ID nr	Category	Research question	Question prioritised
38	Treatment/ symptoms	What treatment is most effective against persistent fever with Covid-19?	
39	Treatment/ symptoms	What treatment is effective against persistent neurological symptoms and cognitive disturbances (such as brain fog, memory loss, difficulty concentrating, fatigue, numbness, tremor, headache) associated with Covid-19?	Carried forward to Questionnaire 2 Then to priority setting meeting, Included in final top list
40	Treatment/ symptom	What treatment is effective for persistent hearing problems associated with Covid-19?	
41	Treatment/ symptom	What is the most effective treatment for persistent gastrointestinal symptoms associated with Covid-19?	
42	Treatment/ symptom	What is the most effective treatment for long-term impaired breathing function/ oxygen uptake or problems with respiratory arrest, associated with Covid-19?	Carried forward to questionnaire 2, then to priority setting meeting and to final top list
43	Treatment/ symptom	What is the most effective treatment for persistent cardiovascular symptoms associated with Covid-19 (including the risk of blood clots)?	Carried forward to Questionnaire 2 then further to priority setting meeting
44	Treatment/ symptom	What is the optimal treatment for persistent cramps and swelling in the diaphragm associated with Covid-19?	
45	Treatment/ symptom	What sort of treatment may be available to relieve coughing and phlegm in the lungs which are symptoms of long-term problems of Covid-19?	
46	Treatment/ selfcare	What are the positive and negative effects of physical training on people with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2
47	Treatment/ selfcare	What selfcare advice helps people with long-term symptoms of Covid-19?	
48	Treatment/ selfcare	What is the effect of different diets/nutritive treatments on long-term symptoms of Covid-19?	
49	Treatment/ selfcare	What is the effect of treatment with vitamins, minerals or antioxidants on people with long-term symptoms of Covid-19?	
50	Treatment	Does treatment need to differ for women, men and possibly children with long-term symptoms of Covid-19?	
51	Children/ treatment	What form of treatment/rehabilitation is most effective for children with long-term symptoms of Covid-19?	
52	Children/ treatment	What complications are children at risk for after they develop long-term symptoms of Covid-19?	

The table continues on the next page

Table 7.1 continued

ID nr	Category	Research question	Question prioritised
53	Children/ treatment	Is there any difference between the long-term symptoms of Covid-19 in children and adults and the underlying causes?	
54	Children/ treatment	What are the symptoms or clinical manifestations of long-term Covid-19 in children	
55	Attitudes/ experiences	How do people with long-term symptoms of Covid-19 describe the attitude of healthcare professionals?	
56	Attitudes/ experiences	How should clinicians' approach and best support people with long-term symptoms of Covid-19?	
57	Attitudes/ experiences	How do people with long-term symptoms of Covid-19 and their relatives perceive their illness (physical and mental function) and its impact on quality of life?	Carried forward to Questionnaire 2
58	Attitudes/ experiences	What effect does the attitude of clinicians have on the course of Covid-19?	
59	Diagnosis/ follow-up	How can an objective diagnosis be made of people with long-term symptoms of covid-19, regardless of whether they have had a positive PCR test during the acute phase, or if they have demonstrable antibodies?	Carried forward to questionnaire 2, further to priority setting meeting, Included in final top list
60	Diagnosis/ follow-up	Can various types of assessment scales aid in determining subjective symptoms in patients with long-term problems after infection with Covid-19?	
61	Diagnosis/ Follow-up	Can expanded diagnosis, to investigate which organs are involved, result in better treatment and eventually prevent future complications in people with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2, then to priority setting meeting, Included in final top list
62	Diagnosis/ Follow-up	What is a reasonable diagnostic procedure to follow for people with long-term symptoms of Covid-19 and what differential diagnoses should be excluded?	Carried forward to Questionnaire 2 and then to priority setting meeting
63	Diagnosis/ follow-up	Should other examinations or investigations be carried out, depending on how long the person has experienced symptoms of Covid-19?	
64	Diagnosis/ follow-up	What effect does being diagnosed with Covid-19 have on the likelihood of receiving treatment for long-term symptoms?	
65	Diagnosis/ follow-up	What follow-up and controls are optimal for people with long-term symptoms of Covid-19?	
66	Complications	Is there a heightened risk of people with long-term symptoms of Covid-19 contracting illnesses (both while the disease is active or after recovery)?	Carried forward to Questionnaire 2 and then to priority setting meeting
67	Sequelae	How many patients are afflicted with secondary complications after suffering long-term symptoms of Covid-19?	

The table continues on the next page

Table 7.1 continued

ID nr	Category	Research question	Question prioritised
68	Sequelae	How do people with long-term symptoms of Covid-19 respond to other infections?	
69	Immunity and vaccination	What is the effect (benefit or risk) of vaccination against Covid-19 for people with long-term symptoms of Covid-19 and does this differ depending on the type of vaccine administered?	Carried forward to Questionnaire 2 and then to priority setting meeting
70	Immunity and vaccination	Is the immune response (e.g. T-cell response, antibodies to Covid-19, development of autoimmunity) different in people with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2 and then to priority setting meeting, Included in final top list
71	Immunity and vaccination	Is it possible to be reinfected even while currently suffering long-term symptoms of Covid-19?	Carried forward to Questionnaire 2
72	Organisation	What facilities do clinicians need to support a return to health and rehabilitation of people with long-term symptoms of covid-19?	
73	Organisation	What is the best means of disseminating information about long-term symptoms of Covid-19 to clinicians and administrative staff who are in contact with patients?	
74	Organisation	What is the best way of organizing care for people with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2 and then to priority setting meeting
75	Organisation	What is the effect of supportive central postcovid-19 teams /specialist clinics for people with long-term symptoms of Covid-19?	
76	Organisation	What is the effect of multidisciplinary teams for people with long-term symptoms of Covid-19?	
77	Organisation	Can adopting procedures from other countries/ international co-operation result in more effective treatment for people with long-term symptoms of Covid-19?	
78	Cause	To what extent is it the virus or the person's own immune response which gives rise to symptoms in those with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2 and then to priority setting meeting
79	Cause	What is the underlying cause of the various patterns of symptoms in people with long-term symptoms of covid-19?	Carried forward to Questionnaire 2, then to priority setting meeting, Included in final top list
80	Cause	Why do the symptoms occur intermittently in people with long-term symptoms of Covid-19?	

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Table 7.1 continued

ID nr	Category	Research question	Question prioritised
81	Cause	Can the virus remain in the body of a person with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2 then to priority setting meeting
82	Cause	Are the long-term symptoms of Covid-19 caused by the same disease mechanism or should they be regarded as several different courses of events?	
83	Prevention of long-term symptoms	What treatment can be given during the acute phase to prevent the development of long-term symptoms of Covid-19?	Carried forward to Questionnaire 2 then to priority setting meeting, included in final top list
84	Association/risk	What is the significance of environmental factors for people in need of rehabilitation after suffering long-term symptoms of Covid-19?	
85	Association/risk	Why do certain people develop long-term symptoms of Covid-19?	Carried forward to Questionnaire 2 then to priority setting meeting, included in final top list
86	Association/risk	Is there a link between previous illness/conditions and long-term symptoms of covid-19?	Carried forward to Questionnaire 2
87	Association/risk	Is there an association between how sick the person was during the acute phase and the occurrence of long-term symptoms of Covid-19?	
88	Other	What risks are associated with premature/rapid return to work for people with long-term symptoms of Covid-19?	
89	Other	Are there similarities between other diseases and long-term symptoms of Covid-19?	
90	Other	What is the cost-benefit of all the research, interventions and treatment strategies for long-term symptoms of Covid-19?	
91	Other	How long is a person with long-term symptoms of Covid-19 infectious?	
92	Other	How can research conducted on hospitalised patients be applied to the group of long-term patients with Covid-19 who were not treated in hospital?	
93	Other	How do the Swedish Social Insurance Agency's regulations and decisions affect recovery and rehabilitation of patients with long-term symptoms of Covid-19?	Carried forward to Questionnaire 2, then to priority setting meeting
94	Other	How are relationships, parenthood and partnerships influenced by long-term Covid-19 symptoms?	
95	Other	How does the language used to describe long-term symptoms after Covid-19 influence how this condition is handled by healthcare system, the Swedish Social Insurance Agency, and employers?	

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Table 7.1 continued

ID nr	Category	Research question	Question prioritised
96	Other	What will be the economic consequences, for patients and society, of long-term symptoms of Covid-19?	Carried forward to Questionnaire 2
97	Other	What is the need for sick leave among people with long-term symptoms of Covid-19?	
100	New	What is the best way of differentiating people with psychosomatic symptoms who seek treatment for long-term symptoms of Covid-19?	
101	New	What are the differences in persistent symptoms, severity of functional incapacity, duration of symptoms, and how many are afflicted, with Post Intensive Care Syndrome (PICS) between those who were infected with Covid-19 and needed intensive care, compared with those who needed intensive care for reasons other than Covid-19?	
102	New	What is the relationship between Postural Orthostatic Tachycardia syndrome (POTS) and long-term symptoms of Covid-19?	
103	New	What is the relationship between hormones and long-term symptoms of Covid-19? For example, related to menopause, menstruation and metabolism.	
104	New	What are the positive and negative effects of treatment based on pressure changes, so-called hyperbaric oxygen treatment?	
105	New	How many people in Sweden have long-term symptoms of Covid-19 and what is the best way of applying the existing diagnostic codes?	
106	New	Is there any method (test, estimate, biomarker) which can be used in the acute phase to predict which patients will develop long-term symptoms of Covid-19?	
107	New	How are people with long-term symptoms of Covid-19 affected by a possible reinfection?	
108	New	How can society progress/ learn from the way the health sector has managed the disease, the treatment decisions, documentation and research with reference to long-term symptoms of Covid-19?	

8 Glossary and Abbreviations

Delphi Method	A panel of people who, independently of one another, anonymously answer a questionnaire multiple times. The repetition gives the participants the opportunity to re-evaluate their answers. The questionnaires are compiled and form the basis of a consensus decision
Evidence	Research results which are systematically searched, assessed for relevance and quality and summarized.
Implementation	A procedure used to introduce new methods or knowledge into everyday routines. Implementation also includes discarding, i.e., less effective methods are abandoned or used less when other methods which have been shown to be more effective are introduced.
Intervention	A measure which is tested, usually treatment for a disease (pharmaceutical, surgical procedure. etc.) or a preventive method.
Consensus	Agreement which is reached by a group of people. Also includes the ethical conditions and the means used to arrive at this agreement.
Practice-oriented research	Research undertaken into procedures applied in the practice of health and medicine, social services and LSS-activity (or new measures which might be introduced). Often two or more measures are compared, to determine their positive and negative effects (e.g. randomised trials and observational studies), but it can also include qualitative studies of experiences.
Primary study	A study in which data are collected on individuals. The term is used to differentiate these studies from secondary studies which involve analysis of data collected from previous studies (for example in a systematic review).
RCT	Randomised controlled trial. An investigation which is both randomised and comparative (controlled).
Systematic overview	Summary of the results of studies on a specifically formulated question, which have been identified by systematic and explicit methods, then selected and critically appraised
Risk of bias	The risk of an error arising in results in the research process, which has occurred in the study design, conduct, assessment of effect, publication or other handling of the results and which is not due to co-incidence
Outcome	In an intervention study, it is the outcome which is ultimately measured.

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Appendix 1

Results of questionnaires

Table 1 Results of questionnaires 1 and 2

ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
		1	2	1	2	1	2	1	2	1	2	1	2	1	2
	Questionnaire	1	2	1	2	1	2	1	2	1	2	1	2	1	2
1	Are there differences in the course of the disease and types of persistent symptoms of Covid-19 between: men and women, people from different age groups, or people of different socioeconomic status (education, income, non-European origin)?	7%	7%	0%	0%	19%	27%	25%	42%	4%	3%	36%	18%	9%	6%
2	How do long-term symptoms of Covid-19 affect the body in people with other underlying health conditions?	6%	–	0%	–	0%	–	0%	–	7%	–	0%	–	6%	–
3	How long can various symptoms of Covid-19 persist and do the different symptoms follow a specific course?	26%	27%	22%	12%	6%	18%	20%	17%	26%	29%	27%	24%	41%	22%
4	How do the type and duration of long-term symptoms of Covid-19 and functional incapacity differ between those who needed intensive care and those who managed with self-care at home?	7%	6%	6%	0%	6%	18%	30%	25%	5%	4%	27%	6%	9%	9%
5	What different kinds of long-term symptoms of Covid-19 occur and what proportion of patients are afflicted by the various symptoms?	25%	26%	33%	35%	38%	55%	40%	42%	21%	23%	45%	24%	44%	34%

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Table xx continued

ID	Question	In total		Relative		Other	Researcher		Patient	Clinicians		Clinicians (or researcher) as well as patient (or relative)			
6	Is there a risk that certain long-term symptoms/ complications of Covid-19 can become chronic?	49%	53%	39%	53%	0%	9%	20%	21%	56%	60%	18%	12%	38%	44%
7	What clinical manifestations occur in persons affected by long-term symptoms of Covid-19?	26%	31%	22%	29%	25%	55%	40%	25%	24%	30%	9%	24%	44%	47%
8	Which psychological symptoms occur in persons with long-term symptoms of Covid-19?	5%	–	0%	–	13%	–	10%	–	5%	–	9%	–	0%	–
9	Which of the long-term symptoms of Covid-19 are potentially serious and which can confidently be allowed to heal themselves?	28%	33%	39%	47%	19%	27%	10%	13%	31%	37%	0%	12%	19%	16%
10	Which long-term symptoms of Covid-19 have the greatest effect on the daily life of patients?	8%	11%	11%	6%	19%	18%	10%	25%	7%	10%	18%	12%	9%	9%
11	What are the positive and negative effects of complementary and alternative treatment methods for people with long-term symptoms of Covid-19?	10%	–	17%	–	0%	–	5%	–	11%	–	0%	–	9%	–

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Table xx continued

ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
12	What are the positive and negative effects of using immunosuppressive drugs in patients with long-term symptoms of covid-19?	13%	–	11%	–	6%	–	10%	–	14%	–	9%	–	9%	–
13	What are the effects of treatment with antiallergenic drugs for people with long-term symptoms of Covid-19?	6%	–	0%	–	0%	–	0%	–	8%	–	0%	–	3%	–
14	What are the positive and negative effects of betablockers on people with long-term symptoms of Covid-19?	3%	–	0%	–	6%	–	0%	–	3%	–	0%	–	6%	–
15	What are the positive and negative effects of steroids/ cortisone and other anti-inflammatory or analgesic drugs on people with long-term symptoms of covid-19?	19%	28%	22%	24%	13%	36%	25%	29%	20%	28%	9%	12%	13%	31%
16	What effects do antibiotics have on people with long-term symptoms of Covid-19?	2%	–	0%	–	0%	–	0%	–	2%	–	0%	–	6%	–
17	What are the effects of antiviral treatment on people with long-term symptoms of covid-19?	12%	–	6%	–	6%	–	5%	–	13%	–	0%	–	13%	–
18	What effects do immunomodulatory drugs have on people with long-term symptoms of Covid-19?	9%	–	11%	–	13%	–	10%	–	7%	–	9%	–	16%	–

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Table xx continued

ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
19	What effects do bronchodilators have on people with long-term symptoms of Covid-19?	5%	–	6%	–	0%	–	0%	–	5%	–	9%	–	9%	–
20	Can the long-term symptoms of Covid-19 be exacerbated by use of certain medication intended for other conditions?	5%	–	17%	–	13%	–	0%	–	5%	–	0%	–	6%	–
21	What is the effect of anticoagulants on people with long-term symptoms of Covid-19?	3%	–	0%	–	6%	–	5%	–	2%	–	0%	–	3%	–
22	What are the effects of ataractic (anti-anxiety) and antidepressant medicine on people with long-term symptoms of covid-19?	1%	–	0%	–	0%	–	0%	–	1%	–	18%	–	0%	–
23	What effects are there, on the course of Covid-19 and on the body, from long-term treatment with analgesics?	2%	–	0%	–	0%	–	0%	–	2%	–	0%	–	6%	–
24	What effect does psychological/psychiatric treatment have on people with long-term symptoms of Covid-19?	2%	–	6%	–	6%	–	10%	–	1%	–	18%	–	0%	–
25	What is the effect of various forms of support for relatives of people with long-term symptoms of Covid-19?	0%	–	0%	–	0%	–	0%	–	0%	–	0%	–	0%	–

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Table xx continued

ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
26	What type of support can people with long-term symptoms of Covid-19 need and can this hasten recovery?	8%	15%	22%	18%	19%	27%	10%	13%	8%	16%	9%	6%	0%	16%
27	Do people with long-term symptoms of Covid-19, who have not required hospitalisation, need the same type of rehabilitation as people who have been hospitalised?	9%	10%	0%	6%	6%	0%	15%	21%	8%	9%	36%	18%	9%	13%
28	How can rehabilitation efforts after long-term symptoms of Covid-19 be optimised and what measures should be included (occupational therapy, physiotherapy, psychology, social worker, speech therapist, dietitian etc.)?	33%	42%	50%	41%	25%	55%	55%	33%	29%	42%	64%	53%	41%	34%
29	What physiotherapy treatment has the best effect on people with long-term symptoms of Covid-19?	10%	11%	6%	12%	6%	36%	5%	8%	9%	11%	36%	12%	19%	13%
30	What interventions should occupational therapists offer people with long-term symptoms of Covid-19?	2%	–	0%	–	0%	–	5%	–	1%	–	18%	–	0%	–
31	What is the effect of cognitive training on people with long-term symptoms of Covid-19?	4%	–	0%	–	6%	–	5%	–	4%	–	9%	–	0%	–

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Table xx continued

ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
32	What rehabilitation/measures are optimal to facilitate return to work for people with long-term symptoms of Covid-19?	11%	13%	6%	0%	13%	0%	10%	29%	10%	13%	36%	29%	9%	13%
33	What is the effect of graded exercise training on people with long-term symptoms of Covid-19?	3%	3%	0%	6%	0%	9%	5%	0%	2%	4%	27%	0%	3%	0%
34	Does pacing work for people with long-term symptoms of Covid-19?	4%	–	11%	–	6%	–	0%	–	3%	–	0%	–	13%	–
35	What is effective treatment for people with long-term symptoms of Covid-19 experiencing disturbed sleep?	5%	–	6%	–	0%	–	0%	–	6%	–	0%	–	6%	–
36	How can the cyclical course of symptoms best be reduced in cases of long-term symptoms of Covid-19?	11%	–	17%	–	6%	–	0%	–	13%	–	0%	–	9%	–
37	What treatment is effective against long-term loss of sense of taste and smell associated with Covid-19?	8%	9%	0%	0%	19%	18%	0%	8%	7%	8%	18%	18%	9%	13%
38	What treatment is most effective against persistent fever with Covid-19?	8%	–	17%	–	0%	–	0%	–	8%	–	0%	–	16%	–

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Table xx continued

ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
39	What treatment is effective against persistent neurological symptoms and cognitive disturbances (such as brain fog, memory loss, difficulty concentrating, fatigue, numbness, tremor, headache) with Covid-19?	38%	53%	61%	82%	38%	45%	30%	54%	39%	54%	18%	47%	25%	41%
40	What treatment is effective for persistent hearing problems associated with Covid-19?	3%	–	0%	–	0%	–	0%	–	3%	–	0%	–	3%	–
41	What is the most effective treatment for persistent gastrointestinal symptoms associated with Covid-19?	5%	–	11%	–	0%	–	0%	–	6%	–	0%	–	6%	–
42	What is the most effective treatment for long-term impaired breathing function/ oxygen uptake or problems with respiratory arrest, associated with Covid-19?	19%	27%	6%	29%	25%	27%	20%	29%	20%	27%	18%	35%	13%	22%
43	What is the most effective treatment for persistent cardiovascular symptoms associated with Covid-19 (including the risk of blood clots)?	16%	22%	17%	29%	19%	18%	15%	13%	17%	24%	18%	6%	9%	19%

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Table xx continued

ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
44	What is the optimal treatment for persistent cramps and swelling in the diaphragm associated with Covid-19?	2%	–	0%	–	0%	–	0%	–	3%	–	0%	–	3%	–
45	What sort of treatment may be available to relieve coughing and phlegm in the lungs which are symptoms of long-term problems of Covid-19?	5%	–	6%	–	0%	–	5%	–	5%	–	0%	–	0%	–
46	What are the positive and negative effects of physical training on people with long-term symptoms of Covid-19?	17%	14%	22%	6%	19%	9%	30%	13%	16%	15%	0%	12%	22%	16%
47	What selfcare advice helps people with long-term symptoms of Covid-19?	10%	–	11%	–	13%	–	5%	–	10%	–	9%	–	9%	–
48	What is the effect of different diets/nutritive treatments on long-term symptoms of Covid-19?	5%	–	6%	–	0%	–	0%	–	6%	–	0%	–	3%	–
49	What is the effect of treatment with vitamins, minerals or antioxidants on people with long-term symptoms of Covid-19?	8%	–	11%	–	0%	–	0%	–	8%	–	0%	–	16%	–
50	Does treatment need to differ for women, men and possibly children with long-term symptoms of Covid-19?	5%	–	11%	–	0%	–	15%	–	4%	–	9%	–	0%	–

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Table xx continued

ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
51	What form of treatment/ rehabilitation is most effective for children with long-term symptoms of Covid-19?	6%	–	6%	–	6%	–	5%	–	7%	–	9%	–	0%	–
52	What complications are children at risk for after they develop long-term symptoms of Covid-19?	6%	–	0%	–	13%	–	0%	–	6%	–	9%	–	0%	–
53	Is there any difference between the long-term symptoms of Covid-19 in children and adults and the underlying causes?	6%	–	0%	–	13%	–	10%	–	5%	–	9%	–	6%	–
54	What are the symptoms or clinical manifestations of long-term Covid-19 in children	3%	–	0%	–	0%	–	0%	–	3%	–	9%	–	3%	–
55	How do people with long-term symptoms of Covid-19 describe the attitude of healthcare professionals?	7%	–	11%	–	6%	–	15%	–	6%	–	0%	–	13%	–
56	How should clinicians' approach and best support people with long-term symptoms of Covid-19?	14%	–	6%	–	6%	–	5%	–	16%	–	0%	–	13%	–
57	How do people with long-term symptoms of Covid-19 and their relatives perceive their illness (physical and mental function) and its impact on quality of life?	4%	12%	0%	24%	19%	9%	15%	25%	2%	10%	0%	12%	6%	16%

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ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
58	What effect does the attitude of clinicians have on the course of Covid-19?	4%	–	0%	–	13%	–	5%	–	4%	–	0%	–	3%	–
59	How can an objective diagnosis be made of people with long-term symptoms of covid-19, regardless of whether they have had a positive PCR test during the acute phase, or if they have demonstrable antibodies?	23%	22%	44%	35%	13%	9%	15%	21%	23%	22%	27%	18%	22%	25%
60	Can various types of assessment scales aid in determining subjective symptoms in patients with long-term problems after infection with Covid-19?	3%	–	0%	–	0%	–	15%	–	2%	–	18%	–	0%	–
61	Can expanded diagnosis, to investigate which organs are involved, result in better treatment and eventually prevent future complications in people with long-term symptoms of Covid-19?	20%	26%	28%	47%	6%	27%	10%	17%	22%	28%	9%	12%	19%	13%
62	What is a reasonable diagnostic procedure to follow for people with long-term symptoms of Covid-19 and what differential diagnoses should be excluded?	16%	19%	33%	24%	31%	36%	5%	17%	13%	18%	36%	29%	25%	13%

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ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
63	Should other examinations or investigations be carried out, depending on how long the person has experienced symptoms of Covid-19?	3%	–	0%	–	6%	–	0%	–	4%	–	9%	–	0%	–
64	What effect does being diagnosed with Covid-19 have on the likelihood of receiving treatment for long-term symptoms?	1%	–	0%	–	0%	–	0%	–	2%	–	0%	–	0%	–
65	What follow-up and controls are optimal for people with long-term symptoms of Covid-19?	11%	–	11%	–	6%	–	5%	–	11%	–	9%	–	9%	–
66	Is there a heightened risk of people with long-term symptoms of Covid-19 contracting illnesses (both while the disease is active or after recovery)?	18%	30%	6%	12%	31%	18%	10%	8%	19%	32%	0%	29%	19%	41%
67	How many patients are afflicted with secondary complications after suffering long-term symptoms of Covid-19?	6%	–	0%	–	6%	–	10%	–	6%	–	9%	–	16%	–
68	How do people with long-term symptoms of Covid-19 respond to other infections?	7%	–	0%	–	0%	–	0%	–	8%	–	0%	–	6%	–

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ID	Question	In total		Relative		Other	Researcher		Patient	Clinicians		Clinicians (or researcher) as well as patient (or relative)			
69	What is the effect (benefit or risk) of vaccination against Covid-19 for people with long-term symptoms of Covid-19 and does this differ depending on the type of vaccine administered?	26%	32%	11%	41%	6%	9%	25%	8%	29%	37%	9%	0%	25%	25%
70	Is the immune response (e.g. T-cell response, antibodies to Covid-19, development of autoimmunity) different in people with long-term symptoms of Covid-19?	14%	30%	0%	0%	19%	27%	10%	21%	16%	33%	9%	24%	13%	19%
71	Is it possible to be reinfected even while currently suffering long-term symptoms of Covid-19?	7%	8%	0%	29%	19%	0%	0%	13%	7%	7%	9%	0%	3%	9%
72	What facilities do clinicians need to support a return to health and rehabilitation of people with long-term symptoms of covid-19?	4%	–	6%	–	13%	–	0%	–	3%	–	9%	–	6%	–
73	What is the best means of disseminating information about long-term symptoms of Covid-19 to clinicians and administrative staff who are in contact with patients?	5%	–	6%	–	0%	–	0%	–	6%	–	0%	–	0%	–

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ID	Question	In total		Relative		Other	Researcher		Patient	Clinicians		Clinicians (or researcher) as well as patient (or relative)			
74	What is the best way of organizing care for people with long-term symptoms of Covid-19?	17%	26%	22%	29%	6%	18%	20%	29%	16%	26%	9%	29%	28%	25%
75	What is the effect of supportive central postcovid-19 teams /specialist clinics for people with long-term symptoms of Covid-19?	3%	–	0%	–	6%	–	5%	–	2%	–	9%	–	3%	–
76	What is the effect of multidisciplinary teams for people with long-term symptoms of Covid-19?	5%	–	6%	–	13%	–	15%	–	3%	–	18%	–	6%	–
77	Can adopting procedures from other countries/ international co-operation result in more effective treatment for people with long-term symptoms of Covid-19?	6%	–	0%	–	13%	–	0%	–	7%	–	0%	–	0%	–
78	To what extent is it the virus or the person's own immune response which gives rise to symptoms in those with long-term symptoms of Covid-19?	19%	27%	6%	29%	13%	18%	20%	21%	22%	28%	0%	12%	6%	22%
79	What is the underlying cause of the various patterns of symptoms in people with long-term symptoms of covid-19?	12%	22%	17%	18%	25%	0%	15%	17%	10%	21%	9%	41%	22%	34%

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ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
80	Why do the symptoms occur intermittently in people with long-term symptoms of Covid-19?	16%	–	0%	–	13%	–	5%	–	18%	–	9%	–	6%	–
81	Can the virus remain in the body of a person with long-term symptoms of Covid-19?	18%	23%	6%	12%	0%	9%	10%	4%	22%	27%	0%	12%	6%	22%
82	Are the long-term symptoms of Covid-19 caused by the same disease mechanism or should they be regarded as several different courses of events?	5%	–	6%	–	6%	–	5%	–	4%	–	18%	–	9%	–
83	What treatment can be given during the acute phase to prevent the development of long-term symptoms of Covid-19?	17%	21%	28%	29%	25%	36%	30%	33%	15%	19%	18%	18%	19%	22%
84	What is the significance of environmental factors for people in need of rehabilitation after suffering long-term symptoms of Covid-19?	1%	–	6%	–	0%	–	0%	–	1%	–	9%	–	0%	–
85	Why do certain people develop long-term symptoms of Covid-19?	24%	31%	17%	29%	6%	45%	50%	46%	22%	28%	18%	29%	41%	47%
86	Is there a link between previous illness/conditions and long-term symptoms of covid-19?	5%	9%	0%	0%	13%	9%	5%	8%	4%	9%	27%	18%	9%	9%

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ID	Question	In total		Relative		Other		Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)	
87	Is there an association between how sick the person was during the acute phase and the occurrence of long-term symptoms of Covid-19?	2%	–	0%	–	6%	–	5%	–	1%	–	0%	–	6%	–
88	What risks are associated with premature/rapid return to work for people with long-term symptoms of Covid-19?	6%	–	0%	–	6%	–	5%	–	7%	–	0%	–	0%	–
89	Are there similarities between other diseases and long-term symptoms of Covid-19?	3%	–	0%	–	13%	–	10%	–	2%	–	0%	–	9%	–
90	What is the cost-benefit of all the research, interventions and treatment strategies for long-term symptoms of Covid-19?	2%	–	0%	–	13%	–	10%	–	1%	–	9%	–	3%	–
91	How long is a person with long-term symptoms of Covid-19 infectious?	5%	–	0%	–	6%	–	10%	–	5%	–	18%	–	6%	–
92	How can research conducted on hospitalised patients be applied to the group of long-term patients with Covid-19 who were not treated in hospital?	2%	–	0%	–	0%	–	0%	–	2%	–	0%	–	6%	–

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ID	Question	In total		Relative		Other	Researcher		Patient		Clinicians		Clinicians (or researcher) as well as patient (or relative)		
93	How do the Swedish Social Insurance Agency's regulations and decisions affect recovery and rehabilitation of patients with long-term symptoms of Covid-19?	13%	13%	28%	41%	19%	9%	20%	13%	12%	12%	9%	12%	6%	9%
94	How are relationships, parenthood and partnerships influenced by long-term Covid-19 symptoms?	2%	–	0%	–	0%	–	0%	–	3%	–	9%	–	0%	–
95	How does the language used to describe long-term symptoms after Covid-19 influence how this condition is handled by healthcare system, the Swedish Social Insurance Agency, and employers?	1%	–	6%	–	0%	–	0%	–	1%	–	0%	–	0%	–
96	What will be the economic consequences, for patients and society, of long-term symptoms of Covid-19?	6%	7%	28%	6%	6%	9%	5%	13%	5%	7%	9%	12%	3%	3%
97	What is the need for sick leave among people with long-term symptoms of Covid-19?	10%	–	11%	–	6%	–	20%	–	10%	–	9%	–	6%	–
100	What is the best way of differentiating people with psychosomatic symptoms who seek treatment for long-term symptoms of Covid-19?	–	6%	–	0%	–	18%	–	13%	–	3%	–	24%	–	13%

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ID	Question	In total	Relative	Other	Researcher	Patient	Clinicians	Clinicians (or researcher) as well as patient (or relative)							
101	What are the differences in persistent symptoms, severity of functional incapacity, duration of symptoms, as well as how many are afflicted, with Post Intensive Care Syndrome (PICS) between those who were infected with Covid-19 and needed intensive care, compared with those who needed intensive care for reasons other than Covid-19?	–	2%	–	0%	–	0%	–	17%	–	1%	–	6%	–	0%
102	What is the relationship between Postural Orthostatic Tachycardia syndrome (POTS) and long-term symptoms of Covid-19?	–	16%	–	24%	–	18%	–	13%	–	15%	–	24%	–	19%
103	What is the relationship between hormones and long-term symptoms of Covid-19? For example, related to menopause, menstruation and metabolism.	–	17%	–	6%	–	0%	–	8%	–	19%	–	0%	–	28%
104	What are the positive and negative effects of treatment based on pressure changes, so-called hyperbaric oxygen treatment?	–	5%	–	0%	–	0%	–	13%	–	5%	–	12%	–	0%

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ID	Question	In total	Relative	Other	Researcher	Patient	Clinicians	Clinicians (or researcher) as well as patient (or relative)							
105	How many people in Sweden have long-term symptoms of Covid-19 and what is the best way of applying the existing diagnostic codes?	–	14%	–	24%	–	9%	–	4%	–	15%	–	6%	–	13%
106	Is there any method (test, estimate, biomarker) which can be used in the acute phase to predict which patients will develop long-term symptoms of Covid-19?	–	11%	–	12%	–	18%	–	29%	–	9%	–	6%	–	16%
107	How are people with long-term symptoms of Covid-19 affected by a possible reinfection?	–	14%	–	12%	–	9%	–	4%	–	15%	–	6%	–	16%
108	How can society progress/learn from the way the health sector has managed the disease, the treatment decisions, documentation and research with reference to long-term symptoms of Covid-19?	–	16%	–	12%	–	27%	–	8%	–	17%	–	12%	–	13%