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# BMJ Open Incidence of cancer-related lymphoedema: a protocol for a living systematic review with meta-analysis

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## ABSTRACT

**Introduction** Given the projected rise in the incidence of cancer treatment-related conditions, such as lymphoedema, and the limited research on lymphoedema in cancers with poor prognoses, there is a need for a better understanding of cancer-related lymphoedema incidence and associated risk factors across all types of cancers. The objectives of this review are (1) to produce a resource on an open-access platform that facilitates continuous update of incidence estimates and risk factors as evidence emerges, (2) to provide the most up-to-date estimate of the incidence of cancer-related lymphoedema and (3) to evaluate the strength and consistency of the association between lymphoedema and cancer treatment and non-treatment-related risk factors.

**Methods and analysis** A living systematic and grey literature search will be conducted to identify studies reporting the incidence, prevalence of lymphoedema or associated risk factors in individuals who have undergone treatment for any type of cancer. Two investigators will independently extract data and assess the risk of bias using the Cochrane Risk of Bias Tool Version 2.0, the Risk of Bias in Non-randomised Studies – of Interventions or the National Institutes of Health Heart, Lung and Blood Institute Study Quality Assessment Tools, depending on study design. The overall strength of evidence will be appraised with the Grading of Recommendations, Assessment, Development and Evaluations tool. Random effect models will be used to produce pooled overall lymphoedema incidence estimates. Subgroup analyses that explore relationships between lymphoedema incidence and lymphoedema measurement method, time since cancer diagnosis and treatment and diagnosis, treatment and behavioural characteristics will be conducted dependent on available data.

**Ethics and dissemination** This living systematic review enables clinicians and researchers to consult a contemporary, comprehensive overview of the incidence of cancer-related lymphoedema and the association between lymphoedema and treatment and non-treatment-related risk factors.

**PROSPERO registration number** CRD42022333291.

## INTRODUCTION

Cancer-related lymphoedema is a pathological swelling of an affected limb or body segment<sup>1</sup>

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This living systematic review will include thorough search methods, searching conventional databases and the grey literature.
- ⇒ Availability of an open-access resource on cancer-related lymphoedema incidence and risk factors that is regularly updated.
- ⇒ Plain-language summaries for patients and clinicians to increase data sharing, translation and implementation of up-to-date information.
- ⇒ Studies that include individuals who have undergone treatment for any type of cancer, and used any method of measuring lymphoedema, will be included.
- ⇒ Likely high turnover of authorship team participating in screening and data extraction over time.

associated with solid tumours, such as melanoma, breast, genitourinary, gynaecological and head and neck cancer, whereby staging or treatment procedures adversely affect the lymphatic system.<sup>1,2</sup> The presence of swelling, fat deposition and fibrosis, lymphoedema-associated symptoms and physical impairments adversely affects function, quality of daily living, work, mental health and social relationships,<sup>3,4</sup> and the presence of lymphoedema has been associated with increased mortality rates in breast cancer survivors.<sup>5</sup> Further, changes in the appearance of the affected area are a constant reminder of cancer, adding to emotional distress, anxiety and depression.<sup>6</sup>

The majority of studies have evaluated breast cancer-related lymphoedema incidence, leading to a 20% incidence estimation.<sup>5,7</sup> However, this incidence estimate is based on findings from a systematic review and meta-analysis conducted more than a decade ago, with changes in breast cancer treatment potentially affecting the contemporary incidence of lymphoedema.<sup>5</sup> In other solid tumours, meta-analysis of cancer-related



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lymphoedema incidence has been limited to head and neck<sup>8,9</sup>, prostate<sup>10</sup> and vulvar<sup>11</sup> cancers with incidence rates reported between 0% and 90%, depending on the cancer type. As such, a need exists to explore current incidence rates of lymphoedema in breast cancer and all other cancer types.

The underlying mechanisms of cancer-related lymphoedema are likely complex and not fully understood. It has been estimated that our current understanding of risk factors accounts for about 35% of the variance observed between those who develop breast cancer-related lymphoedema and those who do not.<sup>3</sup> As such, the ability to predict who will and who will not develop cancer-related lymphoedema remains poor. Cancer-related lymphoedema presents when the demand on the lymphatic transport system exceeds capacity due to tumour-induced, treatment-induced or gene-environment-induced obstruction, damage or impairment to lymphatic function or increased extracellular fluid.<sup>12,13</sup> Several treatment-related risk factors have been identified for upper and lower limb lymphoedema. Lymph node dissection is considered the most consistent and strongest risk factor for lymphoedema. Specifically, the risk of developing upper and lower limb lymphoedema after breast and vulvar cancer increases fourfold (18 studies; 19.9%, 95% CI: 13.5 to 28.2)<sup>5,14</sup> and fivefold (three studies; 32.1%, 95% CI: 20.2 to 44.0),<sup>11</sup> respectively, in patients who underwent axillary/inguinofemoral lymph node dissection compared with sentinel node biopsy. Other characteristics found to have a consistent and meaningful relationship include radiation therapy, higher stage of disease at diagnosis, older age, higher body mass index and insufficient levels of physical activity.<sup>5,11,14</sup> However, changes in treatment observed over the past decades have influenced previously confirmed relationships. For example, the introduction of more targeted radiation therapy in breast cancer has led to an attenuation of risk associated with receipt of radiation therapy for the majority of women diagnosed with early-stage disease, while chemotherapy has emerged as a risk factor.<sup>5,15,16</sup> Beyond age and body mass index, exploration of relationships between demographic and behavioural characteristics (eg, such as place of residence, aeroplane travel, sauna use and physical activity levels) and lymphoedema incidence has been limited to date. With future research attention, understanding of lymphoedema risk factors will continue to evolve.

There is no cure for lymphoedema, and current treatment focuses on management which can be life-long, time-consuming and expensive.<sup>17–19</sup> As such, current best practice recommendations promoted in lymphoedema consensus guidelines<sup>20–23</sup> endorse early diagnosis and subsequent treatment of lymphoedema through prospective surveillance.<sup>24,25</sup> However, cost-effective implementation of prospective surveillance requires identification of (1) those who are most at risk of developing lymphoedema, (2) the most effective timing of assessment (including whether a presurgical measure is required, what frequency of assessment postdiagnosis, if treatment

is cost-effective and length of follow-up), (3) the extent to which the lymphoedema measurement methods and diagnostic thresholds influence understanding of incidence, risk factors and impact of prevention and treatment strategies and (4) the consistency of these relationships across cancer types and over time.

A common criticism of systematic reviews and meta-analysis is that they are out of date quickly.<sup>26</sup> Living systematic reviews allow researchers and clinicians to access one source of information that is assessed on the quality and that is regularly updated (and preferably as open-access content)<sup>26,27</sup> to draw relevant information from for the diagnosis, prevention or management of any given condition.<sup>26,27</sup> As such, the purpose of this living systematic review and meta-analysis is (1) to provide the most up-to-date estimate of the incidence of cancer-related lymphoedema and (2) to evaluate the strength and consistency of the association between lymphoedema and risk factors and (3) to assess whether the incidence and risk factor findings differ by specific factors such as measurement method (eg, diagnostic threshold, timing and frequency of assessment), quality of evidence-base (study design, risk of bias, sample size) and cancer type.

## METHODS

The protocol for this living systematic review with meta-analysis is registered on PROSPERO (CRD42022333291) and follows the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P).<sup>28,29</sup> The current living systematic review will include cancer-related lymphoedema after any type of cancer.

### Research questions

1. What is the incidence of cancer-related lymphoedema across all cancers?
2. What demographic, diagnostic, treatment or behavioural characteristics are associated with lymphoedema incidence?

### Administration of the living systematic review

This living systematic review will be administered as part of Cancer Council Queensland's cancer research programme. After the initial search, which is planned for January 2025, updated searches will be conducted every 6 months over a minimum period of 5 years. The initial manuscript, which will include a detailed data extraction protocol and template, will be conducted as per this protocol and published in a peer-reviewed journal. The data extraction protocol will be updated as evidence emerges to ensure our review stays contemporary. Results of updated searches and the updated overall and subgroup meta-analyses will be made available on Open Science Framework.<sup>30</sup> On this platform, we will also provide a plain-language summary for patients and clinicians to increase data sharing, translation and implementation. An updated manuscript will be written for publication in a peer-reviewed international journal

when (1) new meta-analysis findings change the results, conclusion and/or recommendations and/or (2) every 5 years. If there are any amendments to this protocol, these will be highlighted in the initial peer-reviewed publication and updated in PROSPERO and on Open Science Framework.

### Eligibility criteria

#### Study type

Original research including (randomised) controlled/clinical trials, quasi-experimental, cohort, cross-sectional and case–control studies published in peer-reviewed journals will be eligible for inclusion. Review papers, meta-analyses, editorial or comment papers, case reports, case series or randomised controlled trials that do not report lymphoedema at baseline or lymphoedema for the control group separately will be excluded. No restrictions on the language or origin of papers will be imposed.

#### Participants

Studies that include individuals who are over 18 years old and have undergone treatment for any type of cancer will be considered. Studies of patients with primary lymphoedema will be excluded.

#### Outcomes

Studies reporting the incidence, prevalence or risk factors for secondary lymphoedema will be included.

**Lymphoedema cumulative incidence:** Any method of measured lymphoedema will be included, including but not limited to self-reported swelling/lymphoedema, objectively measured lymphoedema (eg, bioimpedance spectroscopy, circumferences, tissue dielectric constant or magnetic resonance lymphangiography), clinician diagnosis or the use of medical records. Studies reporting self-reported symptoms other than swelling (eg, lymphoedema-associated symptoms such as pain, heaviness and tightness) and do not report on self-reported swelling separately will be excluded, as these symptoms are common postcancer in the absence of lymphoedema.<sup>4</sup> Note that for this review, the point prevalence of lymphoedema will be considered a reasonable estimate of incidence in the absence of precancer treatment lymphoedema status, as the proportion of studies reporting presurgical data is expected to be low.

**Risk factors:** Studies exploring the relationship between any treatment (eg, biological, diagnostic and treatment), non-treatment-related characteristics (eg, demographic, behavioural, lifestyle, socioeconomic and environmental factors) and lymphoedema incidence will be included.

### Information sources and search strategy

A search strategy will be developed for each of the data sources by one author (MP) and an institutional research librarian. An initial search strategy was developed in PubMed and will be modified for each of the electronic databases. The search strategy includes a combination of indexed terms and free-text terms for cancer ('cancer' or 'onco\*' or 'neoplasm\*'), lymphoedema ('lymphoedema'

or 'lymphedema' or 'edema' or 'oedema') and the outcomes of interest ('incidence', 'prevalence', 'risk factor' or 'prognosis'). Full search strategies for all databases and registers, including any filters and limits used, are provided in online supplemental file 1.

#### Conventional databases

Conventional electronic databases PubMed (including MEDLINE), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Science and CINAHL and SPORTDiscus (both via EBSCO) will be searched to identify reports.

#### Identifying grey literature and ongoing studies

We will search for the grey literature on OpenGrey.eu and WorldCat.org. Ongoing studies will be searched for through the following platforms: WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, The European Union Clinician Trials Register and the International Standard Randomised Controlled Trial Number registry of ongoing studies that have not been published. In addition, the included papers will be searched for other possible studies that were not identified by our search.

#### Screening

Search results from the databases will be merged, and duplicates were identified before title and abstract screening. The selection of studies will be performed independently by two authors on the basis of a priori defined eligibility criteria using Covidence. On disagreement, consensus will be sought, and when consensus cannot be reached, a third investigator will decide on eligibility.

#### Data collection and extraction

Data will be independently extracted by two investigators using standardised extraction forms that will be made a priori in Microsoft Excel to establish data extraction, study quality and level of evidence. Disagreements will be resolved by seeking consensus and, if needed, by a third investigator. If study results are not appropriately presented, we will contact the investigators a maximum of three times with 2-week intervals. The following data will be extracted:

- ▶ Publication and study details: study location (country), year of publication, funding source, possible conflicts of interest, study aim, study design (randomised controlled trials, cross-sectional, prospective cohort, retrospective cohort and case–control studies (case–control studies will be only included for risk factor analysis)).
- ▶ Population: sample size, cancer type, time since cancer diagnosis, age, body mass index, interventions (if applicable).
- ▶ Patient eligibility criteria.
- ▶ Outcomes (incidence): time points measured, method of lymphoedema assessment (including but not limited to bioimpedance spectroscopy, tissue dielectric constants, arm circumferences, water

displacement, perometry, lymphoscintigraphy, indocyanine green, clinician diagnosis, patient-reported diagnosis by a clinician or self-reported swelling), diagnostic criteria used to assess lymphoedema, unit of measurement, incidence or point prevalence of lymphoedema.

- ▶ Outcomes (risk factor information): any treatment and non-treatment-related risk factor information, including but not limited to biological and diagnostic (eg, tumour size and metastatic spread), treatment (eg, radiation therapy), demographic (eg, age and place of residence), behavioural and lifestyle (eg, exercise, diet, aeroplane travel and sauna use), socio-economic (eg, socioeconomic status) and other environmental factors (eg, exposure to toxins).
- ▶ Interventions: For the meta-analysis of lymphoedema incidence, we will record results from clinical/randomised trials (all groups and all time points). We will use items from the Template for Intervention Description and Replication (TIDierR)<sup>31</sup> checklist to assure comprehensive data extraction in this section of the extraction form.
- ▶ Data analyses and results: statistical methods, comparisons, outcomes and results (mean (differences), SD/95% CI/SEs).
- ▶ Other information: key conclusion and discussion points.

### Risk of bias

The risk of bias in intervention studies will be assessed using the Cochrane Risk of Bias Tool V.2.0, following the 'intention-to-treat' principle (eg, assignment to the intervention).<sup>32 33</sup> Each study will receive an overall risk of bias score of 'low', 'some' or 'high' across five domains: (1) bias from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome and (5) bias in the selection of the reported results.<sup>32 33</sup> Risk of bias for non-randomised comparative studies will be assessed using the Risk Of Bias in Non-randomised Studies – of Interventions (ROBINS-I).<sup>34</sup> Each study will receive an overall risk of bias score of 'low', 'moderate', 'serious' or 'critical risk' across seven domains: (1) bias due to confounding, (2) bias due to participant selection, (3) bias due to intervention classification, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in the measurement of outcomes and (7) bias in the selection of the reported result.<sup>34</sup>

The risk of bias for observational studies will be assessed using the National Institutes of Health National Heart, Lung and Blood Institute Study Quality Assessment Tools for observational cohort and cross-sectional studies and case-control studies.<sup>35</sup> Each study will receive an overall study quality score of 'good', 'fair' or 'poor', as rated across 14 criteria for observational cohort and cross-sectional studies and 12 criteria for cross-sectional studies.

Two experienced investigators will independently assess the risk of bias. The investigators will trial the assessment approach by assessing 20 (10 intervention, 10 cohort studies) studies related to another prevalent cancer survivorship condition before the study starts (eg, incidence of fatigue postcancer treatment). In case of disagreement between investigators, discrepancies will be discussed, and if consensus is not met, a third investigator will take the decision. All studies will be included in this review regardless of bias. Risk of bias scores will be used to guide the results and discussion of findings.

### Overall strength of evidence

The overall strength of the evidence will be assessed by two independent investigators with the Recommendation, Assessment, Development and Evaluation (GRADE) tool.<sup>36</sup> The GRADE considers the domains of (1) study design, (2) heterogeneity, (3) risk of bias/quality assessment, (4) indirectness, (5) imprecision and (6) publication bias, which were rated as 'not serious', 'serious' and 'very serious' limitations as per the Cochrane recommendations. The overall strength of evidence (GRADE score) will then be rated as 'high', 'moderate', 'low' or 'very low'.

### Data synthesis

The main outcome of interest is the overall cumulative incidence (%) of lymphoedema after diagnosis of cancer. For each risk factor, we will extract ORs, HRs or risk ratios and associated 95% CIs, based on unadjusted results for randomised controlled trials and adjusted estimates obtained from multivariate analyses (ie, controlled for at least one other factor; when available) for other study designs. ReviewManager (RevMan V.5.4) software will be used for all analyses.

We will use a random effects model to produce a pooled overall estimate for lymphoedema incidence and incidence estimates. Meta-analyses including subgroup analyses will be performed depending on available data and will be conducted only when  $\geq 10$  studies are available. Based on the current evidence to date, the following subgroup analyses are planned but not limited to:

- ▶ Cancer type.
- ▶ Lymphoedema stage (staging as defined by the included papers).
- ▶ Lymphoedema location/region (upper limb, lower limb, head and neck, genital or central vs peripheral).
- ▶ Lymphoedema measurement (including but not limited to bioimpedance spectroscopy, tissue dielectric constants, arm circumferences, water displacement, perometry, lymphoscintigraphy, indocyanine green, clinician diagnosis self-reported diagnosis, self-reported swelling and multiple methods (either meeting one or more criteria or meeting multiple criteria)).
- ▶ Time since cancer diagnosis and time since cancer treatment completion (eg, 3 months to <6 months, 6 months to <12 months, 12 months to <24 months, 2 years to <5 years and  $\geq 5$  years).

- ▶ Extent of nodal surgery (number of lymph nodes removed; sentinel-lymph-node biopsy or lymph node dissection).
- ▶ Type of treatment (surgery (type), chemotherapy, radiation therapy).
- ▶ Demographic and behavioural characteristics (eg, age, physical activity levels, body mass index, place of residence, stress levels, aeroplane travel and sauna use).
- ▶ Study design (randomised controlled trials, cross-sectional, prospective cohort, retrospective cohort, case-control).
- ▶ Study quality based on the risk of bias assessments (high, moderate, low).

Because some studies will present more than one estimation of incidence, a hierarchy of decisions has been established to assess which result to include in the overall meta-analysis. For the method of lymphoedema assessment, if studies report a primary outcome or gold standard assessment method of lymphoedema, the data derived from using that method will be used in the overall meta-analysis. When no such primary outcome or gold standard assessment method is reported, results from objective measurement tools will be extracted over self-reported measurement tools, self-reported measurement tools will be extracted over self-reported clinician diagnosis of lymphoedema, and self-reported clinician diagnosis of lymphoedema will be extracted over patient-reported diagnosis of lymphoedema. In the instance that original research identified for inclusion in the meta-analysis has more than one objective measurement or more than one self-reported method of assessment in the absence of a predefined primary outcome/gold standard, the authorship team will extract results from objective circumference measurements as this is the most commonly used method in clinical practice,<sup>37</sup> followed by perometry (which assesses size difference between limbs), followed by bioimpedance spectroscopy (an objective and validated measure),<sup>38</sup> followed by self-report. For time since cancer diagnosis and time since cancer posttreatment completion, results at or closest to 2 years postdiagnosis will be prioritised as evidence to date suggests that most cases (up to 80%) present within 18–24 months postdiagnosis.<sup>39 40</sup> However, it is important to note, our order of priority for specific characteristics (eg, timing of assessment and measurement method) may change as understanding about these factors improves over time.

We will also be conducting subgroup analyses and sensitivity analyses based on study design and study quality to assess the impact of potential bias on incidence and risk factor findings.

## DISCUSSION

This living systematic review with meta-analysis will provide researchers and clinicians with a high-quality, openly accessible source of cancer-related lymphoedema incidence estimates. It will also evaluate the association

between lymphoedema and potential risk factors and assess whether the incidence and risk factor findings differ by specific factors such as measurement methods, quality of evidence-base and cancer type. Importantly, this study design also allows for timely and up-to-date access to new data going forward.

Beyond cancer type, estimation of incidence is challenging as estimates vary based on the measurement method, measurement criterion applied, timing of lymphoedema assessment and study design.<sup>5</sup> This review will include prospective and retrospective studies to ensure the most comprehensive and accurate estimate of lymphoedema incidence and associated risk factors. The included study designs, lymphoedema assessment tools and timing of measurements will influence the accuracy of lymphoedema estimates. In terms of study design, limitations exist for retrospective studies which rely on data recall or information made available from records collected for other purposes (opposed to prospective designs) and for clinical trials/randomised controlled trials who purposefully include biased populations by means of restrictions around recruitment and eligibility. In terms of lymphoedema assessment tools, each assessment tool measures a different attribute(s) of lymphoedema, which will affect estimates. For example, bioimpedance spectroscopy measures the extent of extracellular fluid, whereas circumference measures size (eg, for a limb, this may be volume). Further, the usage of multiple assessment methods is likely to increase the lymphoedema incidence estimate, which is why in this review, only one method of measuring lymphoedema will be included in the meta-analysis, possibly resulting in estimates that are in a more conservative direction. The planned meta-analysis and subgroup analyses of this review will also allow authors to purposely prioritise results drawn from study designs with the lowest level of bias (ie, prospective cohort designs and randomised controlled trials vs retrospective designs) and measurement methods, which will allow authors to quantify the impact of study quality and other relevant characteristics (eg, lymphoedema measurements) on meta-analysis findings.

Since the 2013 systematic review of DiSipio *et al*<sup>5</sup> that established the incidence of breast cancer-related lymphoedema, there have been no further systematic reviews with meta-analysis evaluating risk factors in relation to the incidence of arm lymphoedema including all study designs. Although similar systematic reviews have been conducted in breast cancer-related lymphoedema that solely included cohort studies,<sup>41</sup> lower limb lymphoedema and genital lymphoedema for those with vulvar<sup>11</sup> and prostate cancer,<sup>10</sup> respectively, this type of systematic review has never been conducted to assess the incidence of cancer-related lymphoedema across all cancers. As such, this is the first living systematic review with meta-analysis to assess the incidence and risk factors of all cancer-related lymphoedema across all cancer types. By nature of design, this review will provide clinicians and researchers the ability to obtain regularly updated

knowledge on lymphoedema incidence and risk factor estimates in one open-access source of high-quality information. Further potential challenges that are associated with this type of study design are overcoming resource constraints, potential changes in updating frequencies and managing conflicts of interest. Notwithstanding, this high-quality data source enables health professionals to develop and conduct high-quality research, subsequently improving cancer-related lymphoedema care in terms of diagnostics and management of lymphoedema.

All phases of this work (from conception through to dissemination) will include input from a multi-disciplinary team and engagement with stakeholders. The protocol of this living systematic review has been developed and will be conducted in collaboration with clinicians, researchers and consumers with lived experiences of cancer and/or lymphoedema. The findings of our living systematic review will be presented to stakeholders including clinicians, researchers and consumers to promote the translation of scientific evidence into clinical practice. We will seek the presentation of the study results at national and international conferences, and we will engage with the International Society of Lymphology and the International Lymphoedema Framework for the translation of findings in lymphoedema consensus documents, as well as prevention and management guidelines.

Prospective surveillance to facilitate early detection and management of lymphoedema is currently considered the gold standard lymphoedema treatment as supported by international clinical guidelines.<sup>20–42</sup> This is despite limited evidence supporting the role of prospective surveillance as a means to preventing chronic lymphoedema.<sup>25–43</sup> Further, (cost-effective) implementation of prospective surveillance requires health professionals to make decisions on inclusion of patients, measurement tools and frequency of follow-ups in the limited available time. To improve this prospective surveillance model without overburdening an already pressed healthcare system, identifying those who are most at risk of developing lymphoedema, the most accurate measurement techniques and the most effective timing of assessment is essential. This living systematic review will refine prospective surveillance models by providing up-to-date incidence and associated risk factor evidence for all cancer types (including subgroup analyses on lymphoedema measurement, stage of lymphoedema and time since diagnosis), which are likely to change in strength and direction as a consequence of advances in oncology technology and treatment options. The intent is for researchers and clinicians to use findings from this work to assist timely refinement of lymphoedema prevention, early diagnosis and management strategies and consensus guidelines and to help guide implementation of these guidelines into clinical practice.

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**Contributors** MP, BS and SH came up with the study idea and designed the study. MP, SH and KB designed the statistical analyses plan. MP developed the search with the help of a research librarian. MP and SH drafted the first version of the manuscript. All authors provided feedback and gave important intellectual input. All authors read and consented to the content of the article. MP is the guarantor of this work.

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