SPONSORED RESEARCH COLLABORATION AGREEMENT

This Agreement is made this 1st day of May 2020 (the "Effective Date"), between The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030 ("MD Anderson"), a member institution of The University of Texas System ("UTSystem"), Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030 ("BCM"), Texas A&M University Health Science Center, 301 Old Main Dr., College Station, Texas 77843 ("TAMHSC"), a health related entity of Texas A&M University, a member of the The Texas A&M University System ("TAMUS") and Cedars-Sinai Medical Center 8700 Beverly Blvd., Los Angeles, CA 90048 ("CSMC"). Each party is hereinafter referred to as a "Collaborator." The Collaborators hereby agree as follows:

RECITALS

A. The Collaborators are interested in collaborating on a clinical study (the "Study") under a protocol entitled "*BADAS: BACILLUS CALMETTE-GUÉRIN VACCINATION AS DEFENSE AGAINST SARS-CoV-2. A RANDOMIZED PLACEBO-CONTROLLED TRIAL TO PROTECT HEALTH CARE WORKERS BY ENHANCED TRAINED IMMUNE RESPONSES*" as described in Exhibit A, and as may be amended from time to time, subject to the approval of each Collaborator's institutional review board(s) ("Protocol").

B. As the Study progresses, additional sites may be interested in joining the collaboration, and such additional sites may join on to this Agreement as set forth in this Agreement.

C. Each Collaborator shall appoint a principal investigator at its site (each, a "Collaborating Investigator") to oversee the performance of the Study under the Protocol at such Collaborator's facilities. BCM's Collaborating Investigator is Andrew DiNardo. TAMHSC's Collaborating Investigator is Jeffrey Cirillo. MD Anderson's Collaborating Investigator is Ashish Kamat CSMC's Collaborating Investigator is Moshi Arditi, MD.

D. The Collaborators each agree that Collaborator and their Collaborating Investigators shall perform the Study under the Protocol subject to the terms and conditions of this Agreement and approval of each party's institutional review board.

1. PROTOCOL AND STUDY

1.1 Each Collaborator shall conduct the Study, as an independent contractor, in accordance with Collaborator's institutional policies, applicable laws, regulations, and guidelines and in strict accordance with the Protocol, as approved by such Collaborator's institutional review board (the "IRB"). Each Collaborator will recruit Study subjects in accordance with the Protocol. The Study is exempt from filing an Investigational New Drug Application ("IND") in accordance with U.S. Food and Drug Administration ("FDA") requirements as reflected in the IND exemption determination letter from the FDA dated March 30, 2020 ("FDA Exemption Letter"). The Study at each Collaborator site will be supervised by the Collaborating Investigator at such Collaborator, with assistance from associates and colleagues as required. Deviations from the Protocol may be made if (i) necessary to protect the safety of Study subjects, or (ii) required by Collaborator's IRB.

1.2 TAMHSC will provide funding ("Funding") to the other Collaborators in accordance with Exhibits B,C and D. Subject to budgets in these exhibits, expenses will be payable upon invoice sent to TAMHSC by the respective Collaborator. For any subsequent parties that wish to join as Collaborators ("Subsequent Collaborators"), these will be added through an amendment to this Agreement.

1.3 Nothing in this Agreement will limit or prohibit any Collaborator or any of their respective personnel, including any Collaborating Investigator, from conducting any research or for performing research for or with any entity or person, including any other outside sponsors. The parties acknowledge that this provision is intended to preserve the academic freedom and integrity of the Collaborators and their respective faculty members.

2. CONDUCT OF THE STUDY

2.1 Each Collaborator shall submit patient and/or regulatory data timely in accordance with and as instructed in the Protocol, including but not limited to, breaches of the Protocol of which any Collaborator becomes aware.

2.2 Each Collaborator will have its own regulatory responsibility for the Study and for such Collaborator's conduct of the Study.

2.3 Each Collaborator and Collaborating Investigator shall obtain informed consent of all Study subjects at its site in accordance with 21 CFR Part 50 and/or other applicable laws and regulations. Further, each Collaborator shall obtain IRB review and approval of the Protocol, including the informed consent form, in accordance with 21 CFR Part 56 and/or other applicable laws and regulations. Collaborator shall supply TAMHSC with evidence of IRB approval prior to receipt of funding.

2.4 Each Collaborator agrees to comply with any and all applicable laws relating to patient privacy. Each Collaborator shall take any and all reasonable and ethical actions necessary to ensure that it will be able to provide and share all Study related data to the other Collaborators, such acts including, without limitation, obtaining in a manner consistent with the Health Insurance Portability and Accountability Act of 1996 and the regulations promulgated thereunder ("HIPAA"), authorization from each Study subject to provide "Protected Health Information" (as defined under HIPAA) regarding such Study subjects to TAMHSC, MD Anderson, BCM, and CHSH.

2.5 Each Collaborator shall submit written reports to TAMHSC summarizing the current status of the Study every six (6) months after initiation of the Study at Collaborator. The format and detail of said written reports shall be according to the mutual understanding and agreement between the TAMHSC Investigator and the Collaborator Investigator.

2.6 Upon completion of the Study at each Collaborator or upon earlier termination as set forth in Section 4.1, each Collaborator shall submit a final written report to the other Collaborators including all relevant information concerning its conduct of the Study, such final report as agreed upon between the Collaborating Investigators.

2.7 Each Collaborator shall respond to inquiries by TAMHSC and the TAMHSC Investigator regarding the conduct and status of the Study, and shall cooperate with TAMHSC and TAMHSC Investigator in providing any necessary information regarding financial records or data and results related to the Study, if requested by an administrative authority.

3. TRANSFER OF MATERIALS AND DATA

3.1 Depending on each Collaborator's participation in the Study, each Collaborator may be providing certain data and biological samples to another Collaborator as set forth in the Protocol.

3.2 The FDA-approved TICE® Bacillus Calmette-Guérin ("BCG"), for intravesical use, BCG LIVE strain of the Merck BCG vaccine shall be the study drug ("Study Drug"). Receipt, storage, and handling of

Study Drug will be in compliance with all applicable laws and regulations, the Protocol, and the FDA Exemption Letter.

3.3 MD Anderson may provide, to the extent MD Anderson has excess supplies, to TAMHSC, certain quantities of properly-labeled Study Drug, including but not limited to, handling and storage instructions, solely for TAMHSC to conduct the Study in accordance with the Protocol, and not for any other purpose. TAMHSC acknowledges that MD Anderson purchased the Study Drug from a commercial supplier, and if necessary, supplies of the Study Drug may also be purchased by the TAMHSC as needed. TAMHSC may not distribute or release the Study Drug to any person or entity other than personnel under the TAMHSC Investigator's direct supervision, and TAMHSC shall ensure that no one will be allowed to take or send the Study Drug to any other location, unless written permission is obtained from MD Anderson or except as set forth in the Protocol. TAMHSC acknowledges that the Study Drug provided by MD Anderson is experimental in nature and it is provided WITHOUT WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED. MD ANDERSON MAKES NO REPRESENTATION OR WARRANTY WITH RESPECT TO THE STUDY DRUG, INCLUDING BUT NOT LIMITED TO ANY REPRESENTATION OR WARRANTY THAT THE USE OF THE STUDY DRUG WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT.

3.4 In the event any biological samples collected by a Collaborator pursuant to the Protocol is shared with another Collaborator (the "Collaborator Materials"), the following terms and conditions shall apply with respect to such Collaborator Materials:

a. Such Collaborator Material is considered proprietary to the providing Collaborator.

b. Such Collaborator Materials shall only be used by the receiving Collaborator for the purposes of the Study and will not be used for any other purpose.

c. The receiving Collaborator may not distribute, release, or in any way disclose such Collaborator Material to any person or entity other than personnel under the receiving Collaborating Investigator's direct supervision, and the receiving Collaborator shall ensure that no one will be allowed to take or send such Collaborator Material to any other location, unless written permission is obtained from the providing Collaborator or except as set forth in the Protocol.

d. The receiving Collaborator shall have no rights in such Collaborator Material other than as provided in this Agreement. At the request of the providing Collaborator, the receiving Collaborator will return all such Collaborator Material.

e. The Collaborator Material is experimental in nature and it is provided WITHOUT WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED. THE PROVIDING COLLABORATOR MAKES NO REPRESENTATION OR WARRANTY WITH RESPECT TO THE MATERIAL, INCLUDING BUT NOT LIMITED TO ANY REPRESENTATION OR WARRANTY THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT.

3.5 In the event any data collected by a Collaborator pursuant to the Protocol is shared with another Collaborator (the "Collaborator Data"), the following terms and conditions shall apply with respect to such Collaborator Data.

a. Such Collaborator Data is considered proprietary to the providing Collaborator, provided, however, each Collaborator acknowledges and agree that once such Collaborator Data has been

aggregated with other Collaborator Data, such Collaborator Data will remain part of the aggregated data and cannot be extracted from the aggregated data.

b. Such Collaborator Data shall only be used by the receiving Collaborator for the purposes of the Study and will not be used for any other purpose.

c. The receiving Collaborator may not distribute, release, or in any way disclose such Collaborator Data to any person or entity other than personnel under the receiving Collaborating Investigator's direct supervision, and the receiving Collaborator shall ensure that no one will be allowed to take or send such Collaborator Data to any other location, unless written permission is obtained from the providing Collaborator or except as set forth in the Protocol.

d. In the event the informed consent and written authorization for a Collaborator site does not authorize the sharing of Protected Health Information with a Subsequent Collaborator and such Collaborator Data constitutes a Limited Data Set (as defined under HIPAA), Subsequent Collaborator agrees to use the Data Use Agreement attached hereto as Exhibit E to facilitate the transfer of the Limited Data Set as required under 45 C.F.R. § 160.514(e)(4). In the event the informed consent and written authorization for a Collaborator site does not authorize the sharing of Protected Health Information ("PHI") with a Subsequent Collaborator, the Subsequent Collaborator shall only use any PHI received from such Collaborator site in accordance with the terms of this Agreement, the informed consent and written authorization, and applicable laws.

e. The Collaborator Data is experimental in nature and it is provided WITHOUT WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED. THE PROVIDING COLLABORATOR MAKES NO REPRESENTATION OR WARRANTY WITH RESPECT TO THE MATERIAL, INCLUDING BUT NOT LIMITED TO ANY REPRESENTATION OR WARRANTY THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT.

4. TERM

4.1 This Agreement shall continue in force until the earlier of completion of the Study as mutually agreed upon by the parties or thirty-six (36) months from the Effective Date; provided, however, that the parties may extend the term of the Agreement by mutual written agreement. Any party may terminate the Agreement by giving sixty (60) days advance notice to the other parties. In case of such termination by a single party, the Agreement may continue for the non-terminating parties. Notwithstanding the foregoing, any Collaborator may immediately terminate this Agreement with respect to its own participation:

a. in the event of termination of the Study by the FDA or any other governmental or regulatory authority; or

b. for safety, regulatory, or ethical reasons; or

c. by mutual written agreement between the Collaborators.

d. In the event of revocation of the Funding for the Study.

Further, the other Collaborators may immediately terminate the Agreement with respect to a Collaborator if (a) such Collaborator breaches a material provision of this Agreement; (b) the Collaborating Investigator for such Collaborator is no longer able to conduct the Study under this Agreement and such Collaborator is unable to find a substitute investigator; (c) a Collaborator or

Collaborating Investigator fail to perform the Study in accordance with applicable laws, regulations, guidelines and the Protocol; or (d) upon the occurrence of any event identified in the Protocol as constituting grounds for terminating the Study.

Upon any such immediate termination event, the Collaborators terminating the Agreement shall promptly provide written notice of such termination to the terminated Collaborator. Any terms that by their nature would survive expiration or termination of this Agreement shall survive any such expiration or termination.

5. RECORD KEEPING

5.1 Each Collaborator shall maintain adequate and accurate records relating to its conduct of the Study. Each Collaborator shall maintain all such records as required pursuant to any applicable law or regulation, but no less than one (1) year following the completion of the Study.

5.2 Each Collaborator represents and certifies that, to the best of its knowledge and belief, as of the effective date of this Agreement, there is no pending regulatory audit, investigation or proceeding involving such Collaborator, or its Collaborating Investigator relating to compliance with laws regarding the conduct of any clinical research, nor have any of the foregoing been debarred under 21 U.S.C. Section 335(a) or (b), nor disqualified under 21 C.F.R. Section 312.70 or Section 812.119, nor excluded or debarred from participation in any Federal health care program as defined in 42 U.S.C 1320a-7b(f). If any Collaborator, or any employee, officer or director of the such Collaborator, is excluded or debarred from participation in any Federal health care program or other government payment program, or becomes otherwise ineligible to participate in any such program, such Collaborator shall promptly notify the other Collaborators after such event. Upon the occurrence of such event, whether or not such notice is given to the other Collaborators, the other Collaborators may immediately terminate this Agreement.

5.4 If a Collaborator receives either (a) notice from the FDA or other government agency that such agency plans to conduct an investigation at Collaborator covering, in whole or in part, data or other activities relating to the Study, or (b) an inquiry from the FDA or other government agency regarding, in whole or in part, data or other activities relating to the Study, then Collaborator shall immediately notify the other Collaborators.

5.5 During and for a period of at least two years after completion of the Study, each Collaborator shall promptly report to the other Collaborators and Collaborator Investigators any information that could directly affect the health or safety of past or current subjects or influence the conduct of the Study, including but not limited to the study results and information in site monitoring reports and data safety monitoring committee reports as required by the protocol. In each case the Investigator and all Collaborators shall be free to communicate these findings to each study subject and their IRB.

6. INDEMNIFICATION AND INSURANCE

6.1 Each Collaborator shall be responsible for its own negligent acts or omissions and the negligent acts or omissions of its employees, officers, or directors, to the extent allowed by law.

6.2 Each Collaborator shall maintain a program of commercial insurance or self-insurance in full force and effect during the term of this Agreement with coverage necessary to meet its liability

obligations under this Agreement and in accordance with laws applicable to such Collaborator. MD Anderson, as a member institution of UTSystem, is an agency of the State of Texas and is self-insured pursuant to The University of Texas System Professional Medical Malpractice Self-Insurance Plan, under the authority of Section 59.01, Texas Education Code. TAMHSC, as a member of TAMUS, is an agency of the State of Texas and is self-insured up to the limits of liability set in the Texas Tort Claims Act.

6.3 **NO PARTY SHALL BE LIABLE TO ANOTHER PARTY HEREUNDER FOR SPECIAL, INDIRECT, OR CONSEQUENTIAL DAMAGES ARISING OUT OF OR IN CONNECTION WITH THIS AGREEMENT, EVEN IF ADVISED OF THE POSSIBILITY OF THE SAME.**

7. PUBLICATION AND CONFIDENTIALITY

7.1 The parties have the right to publish or otherwise make public the results of the Study (the "Research Results"). All parties acknowledge that the Research Project is collaborative, and that a joint publication is anticipated to be authored by all Collaborating Investigators, as appropriate based on generally accepted standards for academic and scientific publications. Therefore, the parties agree not to independently publish the final Research Results before the publication of the multi-investigator paper; but in no event shall the parties be so restricted after the expiration of twelve (12) months from completion of the Study at all sites. If no joint publication has been submitted for publication after twelve (12) months from the completion of the Study at all sites, the parties reserve the right to independently publish the Research Results, with due regard to the protection of all other party's Confidential Information, provided, however, that this due regards shall not prevent such party from publishing the Research Results. The party wishing to publish will submit the manuscript of any proposed publication to the other parties at least thirty (30) days before publication, and the other parties shall have the right to review and comment upon the publication in order to protect its Confidential Information. Upon request, the publication will be delayed up to sixty (60) additional days to enable any reviewing party(ies) to secure adequate intellectual property protection of property of such reviewing party(ies) that would be affected by said publication. Notwithstanding the foregoing, a party may independently publish or otherwise make public preliminary reports and analyses of data, and description of technologies prior to the final multi-investigator paper following seven (7) days from date of notification to the other parties. If the publication comes about, the parties agree to acknowledge all Collaborating Investigators, as academically and scientifically appropriate, based on provision of the Collaborator Material and Collaborator Data or other direct contribution to the Study.

7.2 Except as otherwise required by law or regulation, by applicable publishing or academic policy, or for the purpose of acknowledging the contribution of any other party to the Study, no party shall release or distribute any materials or information containing the name of any other party or any of its employees without prior written approval by an authorized representative of the non-releasing party.

7.3 In connection with the conduct of the Study, the parties may wish to disclose confidential information to one other ("Confidential Information"). In order for the Collaborators to appreciate when non-public information is being conveyed, to the reasonable extent possible, information disclosed in tangible form shall be clearly identified at the time of disclosure as being Confidential Information by an appropriate and conspicuous marking. Similarly, to the reasonable extent possible, information disclosed in intangible form (e.g., oral or visual) shall be identified as being Confidential Information at the time of disclosure, and shall be confirmed as such in writing to the other Collaborators within 30 days after such disclosure. Notwithstanding the foregoing, any failure by a Collaborator to mark documents confidential or to reduce oral disclosures to writing will not relieve the receiving party of its obligations herein if by the nature of the information, would reasonably constitute proprietary or Confidential Information. Every party will use reasonable efforts to prevent the disclosure of any other party's Confidential Information to third

parties who are not parties to this Agreement for a period of five (5) years from receipt thereof, provided that the receiving party's obligation shall not apply to information that:

a. is already in the receiving party's possession at the time of disclosure thereof;

b. is or later becomes part of the public domain through no wrongful act or omission of the receiving party;

c. is received from a third party having no obligations of confidentiality to the disclosing party;

d. is independently developed by the receiving party as evidenced by the receiving party's written records; and

e. is required by law or regulation to be disclosed, provided that (i) to the extent reasonably possible the receiving party first provides the disclosing party with reasonable advance written notice and the opportunity, if possible, to limit, object to, or narrow such disclosure; (ii) to the extent practicable, the receiving party seeks confidential treatment of such information by protective order or otherwise; and (iii) any disclosure hereunder is limited in scope and recipients to that which is legally required.

7.4 If in conjunction with the Study any party obtains any health or medical information of any individual from another party, the receiving party will hold in confidence the identity of the individual and the health/medical information of such individual, will comply with applicable laws, policies, and the Protocol regarding the confidentiality of such information, and will not disclose or use any such information except as authorized by the individual's informed consent and/or authorization (if applicable) and as authorized by an applicable IRB and/or by this Agreement.

8. INTELLECTUAL PROPERTY RIGHTS

8.1 "Inventions" means all inventions or discoveries conceived or invented during the conduct of the Study and arising from the performance of the Study under this Agreement. The parties shall promptly notify each other in writing of, and provide a detailed written description of any Inventions, such disclosure being considered Confidential Information of the providing Collaborator. Ownership of Inventions will be determined by inventorship and inventorship will be determined in accordance with United States patent law (whether or not patentable).

9. GENERAL

9.1 This Agreement, including any and all attachments hereto, constitutes the entire and only Agreement between the parties relating to the Study, and all prior negotiations, representations, agreements, and understandings are superseded hereby. No agreements altering or supplementing the terms hereof, including the exhibits attached hereto, may be made except by a written document signed by the duly authorized representatives of the parties.

9.2 Any conflicts or inconsistencies between the Protocol and this Agreement are controlled by this Agreement, provided, however, that the parties acknowledge that the Protocol is intended to govern medical and subject care matters related to the Study, and the Agreement is intended to govern business and legal matters related to the Study.

9.3 This Agreement shall be construed and enforced in accordance with the laws of the State of Texas, United States of America.

9.4 Any notice required to be given under this Agreement shall be sent to the other party by overnight delivery, by facsimile (with written confirmation of transmission), or by certified mail, return receipt requested; and such notice shall be deemed given, in the case of overnight delivery, the day following delivery to the carrier or, in the case of facsimile, the day transmitted or, in the case of certified mail, 3 days after the date of postmark. Notice shall be given to each party as follows:

To MD Anderson:

Attention: Chief Legal Officer
The University of Texas M.D. Anderson Cancer Center
1515 Holcombe Blvd, Unit. 1674
Houston, Texas 77030

With a copy to:
Executive Director, Sponsored Programs
The University of Texas M.D. Anderson Cancer Center
1515 Holcombe Blvd., Unit 1676
Houston, Texas 77030

To TAMHSC:

Texas A&M University
Research Administration
Attn: Travis Young, Ph.D.
301 Old Main Drive, Suite 3104 ILSB
College Station, TX 77843-1260
Email: negotiations@tamu.edu

With a copy to:
Texas A&M University Health Science Center
Center for Airborne Pathogen Research and Tuberculosis Imaging (CAPRI)
Attn: Dr. Jeffrey Cirillo, Director
Department of Microbial Pathogenesis and Immunology
Medical Research & Education Building, Room #3012
8447 State Hwy 47
Bryan, TX 77807
Email: jdcirillo@medicine.tamhsc.edu

To BCM:

Baylor College of Medicine
Attn: Sponsored Programs Office
Baylor College of Medicine
1 Baylor Plaza BCM 310
Houston, TX 77030
spo@bcm.edu

With a copy to:
Baylor College of Medicine
Attn: Andrew R. DiNardo, MD
Assistant Professor
Infectious Diseases
Global and Immigrant Health

1102 Bates, St,
Office: Suite 630.61
Lab: Suite 330
Email: Andrew.DiNardo@bcm.edu

To CSMC:

Cedars-Sinai Medical Center
Office of Research Administration
Attn: Lloyd Dysim
8700 Beverly Blvd. 65-WILS #1150
Los Angeles, CA 90048
Email: Lloyd.dysim@cshs.org

With copy to:
Cedars-Sinai Medical Center
Attn: Moshe Arditi, MD
Pediatrics, Division of Infectious Diseases
8700 Beverly Blvd.
Los Angeles, CA 90048
Email: moshe.arditi@cshs.org

9.5 This Agreement may not be assigned, in whole or in part, by any party without the other parties' prior written consent.

9.6 All parties shall comply with any Export Controls applicable to the conduct of the Study and/or to this Agreement.

9.7 The waiver from time to time by either party of any of its rights or its failure to exercise any remedy shall not operate or be construed as a continuing waiver of some or of any other of such party's rights or remedies provided in this Agreement.

9.8 Each party shall be temporarily relieved of its obligations to the extent that fulfillment of such obligations shall be prevented by unforeseeable events beyond the reasonable control of the party affected (such as war, terrorist attack, fire, lightning, earthquake, flood, tsunami, blizzard, tornado and other acts of God), but only for the duration of the unforeseeable event. Notwithstanding anything to the contrary, the parties agree and acknowledge that obligations under this Agreement may be delayed due to the infectious public health crisis in effect at or around the execution of this Agreement. In the event that obligations under this Agreement are accordingly delayed, the delayed party will promptly notify the non-delayed parties of any material delay in commencing or continuing the Study.

9.9 Each party represents and agrees that it is not a party and will not be a party to any agreement that conflicts with any obligations or provisions of this Agreement.

9.10 Nothing in this Agreement is intended or shall be deemed to constitute an agency, joint venture, partnership, employer-employee or fiduciary relationship between the Parties. All activities by each party hereunder shall be independent acts of each party except as otherwise specifically provided herein. No party shall incur any debts or make any commitments for the other party, except as may be expressly provided herein.

9.11 MD Anderson is an agency of the State of Texas and under the constitution and laws of the State of Texas possesses certain rights and privileges and only such authority as is granted to it under the constitution and laws of the State of Texas. TAMHSC is an agency of the State of Texas and under the constitution and laws of the State of Texas possesses certain rights and privileges and only such authority as is granted to it under the constitution and laws of the State of Texas. Notwithstanding any provision hereof, nothing herein is intended to be, nor will it be construed to be, a waiver of the sovereign immunity of the State of Texas or a prospective waiver or restriction of any of the rights, remedies, claims, and privileges of the State of Texas.

9.12 No party will be required to perform any act or to refrain from any act in violation of any applicable state or federal law. In this regard, this Agreement is subject to, and the Parties agree to comply with, all applicable local, state, and federal laws, statutes, rules, and regulations, and all applicable judicial or administrative orders. Any provision or any law, statute, rule, regulation, or order that invalidates any provision of this Agreement, that is inconsistent with any provision of this Agreement, or that would cause one or both of the Parties hereto to be in violation of law will be deemed to have superseded the terms of this Agreement. The Parties, however, will use their reasonable efforts to accommodate the terms and intent of this Agreement to the greatest extent possible consistent with the requirements of the law and negotiate in good faith toward amendment of this Agreement in such respect.

9.13 This Agreement may be executed in counterparts, which taken together shall constitute one single representation between the Parties.

[*Signature page to follow*]

IN WITNESS WHEREOF, the undersigned hereby enter into this Agreement, effective as of the Effective Date.

The University of Texas
M. D. Anderson Cancer Center

DocuSigned by:
By: Amy Moritz
6257A58DD91941A...

Name: Amy Moritz
Title: Assistant Director, Reseach Administration

Read and Understood:

DocuSigned by:
By: Ashish Kamat 5/22/2020
D897792654D94DF...
Collaborating Investigator

Reviewed and Approved by UTMDACC Institutional Review Board

#58428

Baylor College of Medicine

By: Leanne Scott

Name: Leanne Scott, PhD
Title: Sr. Director Sponsored Programs

Read and Understood:

By: Andrew DiNardo
Collaborating Investigator

Texas A&M Health Science Center,
a health related entity of
Texas A&M University

By: Katherine V. Kissmann 5.12.2020

Name: Katherine V. Kissmann
Title: Director of Research Contracts

Read and Understood:

By: Jeffrey D. Cirillo Digitally signed by Jeffrey D. Cirillo Date: 2020.05.11 20:29:44 -05'00'
Collaborating Investigator

Cedars-Sinai Medical Center

By:

Name: Lloyd Dysim
Title: Principal Grant & Contract Officer

Read and Understood:

By: Moshe Arditi, MD (PI)
Collaborating Investigator

EXHIBIT A

BACILLUS CALMETTE-GUÉRIN VACCINATION AS DEFENSE AGAINST SARS-CoV-2.
A RANDOMIZED CONTROLLED TRIAL TO PROTECT HEALTH CARE WORKERS BY ENHANCED TRAINED IMMUNE RESPONSES

PROTOCOL TITLE:

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BACILLUS CALMETTE-GUÉRIN VACCINATION AS DEFENSE AGAINST SARS-CoV-2. A RANDOMIZED CONTROLLED TRIAL TO PROTECT HEALTH CARE WORKERS BY ENHANCED TRAINED IMMUNE RESPONSES

Protocol ID: BADAS

Protocol Version: 1.4

Date: 04 April 2020

Principal Investigators Andrew DiNardo, MD
Baylor College of Medicine (BCM), Houston, TX

Ashish M. Kamat, MD, MBBS
MD Anderson Cancer Center (MDAC), Houston, TX

Megan Murray MD, DPH
Harvard School of Public Health, Boston, MA

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
BCG	**Bacillus Calmette-Guerin**
BCM	**Baylor College of Medicine**
CA	**Competent Authority**
CFR	**Case Fatality Rate**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
FDA	**Food and Drug Administration**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
HCW	**HealthCare Workers**
IB	**Investigator’s Brochure**
ICD	**Informed Consent Document**
ICF	**Informed Consent Form**
ICU	**Intensive Care Unit**
IMP	**Investigational Medicinal Product**
IRB	**Institutional Review Board**
IMPD	**Investigational Medicinal Product Dossier**
MDACC	**M.D. Anderson Cancer Center**

NSE	**Non specific effects**
PCR	**Polymerase chain reaction**
(S)AE	**(Serious) Adverse Event**
SARS-CoV-2	**Severe Acute Respiratory Syndrome Coronavirus-2**
Sponsor	**The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator (Sponsor-Investigator). A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.**
RNA	**Ribonucleic acid**
PBMC	**Peripheral blood mononuclear cell**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TAMU	**Texas A&M University**
UP	**Unanticipated Problem**
WHO	**World Health Organization**

SUMMARY

Rationale: SARS-CoV-2 spreads rapidly throughout the world. A large epidemic would seriously challenge the available hospital capacity, and this would be augmented by infection of healthcare workers (HCW). Strategies to prevent infection and disease severity of HCW are, therefore, desperately needed to safeguard continuous patient care. Bacille Calmette-Guérin (BCG) is a vaccine against tuberculosis, with protective non-specific effects against other respiratory tract infections in *in vitro* and *in vivo* studies, and reported morbidity and mortality reductions as high as 70%. Furthermore, in our preliminary analysis, areas with existing BCG vaccination programs appear to have lower incidence and mortality from COVID19[1]. We hypothesize that BCG vaccination can reduce HCW infection and disease severity during the epidemic phase of SARS-CoV-2.

Objective: Primary objective: To measure the efficacy of BCG vaccination among HCW in preventions infection with CARS-CoV2 . Secondary objective: To measure the efficacy of BCG vaccination among HCW in mitigating the severity of COVID19.

Study design: A placebo-controlled adaptive multi-centre randomized controlled trial.

Study population: High risk HCW with direct patient contacts, defined as physician assistants, respiratory therapists, nurses, physicians or other HCWs working at emergency rooms, ICUs and in locations within hospitals where COVID-infected patients are treated.

Intervention: Participants will be randomized between intradermal administration of BCG vaccine or placebo in a 1:1 ratio.

Study endpoints: Primary endpoint: incidence of SARS-CoV2 infection following BCG vaccination compared to placebo. Secondary endpoint: COVID19-related disease severity following BCG vaccination compared to placebo.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Based on previous experience and randomized controlled trials in adult and elderly individuals, the risks of BCG vaccination are considered low. The objective of this trial is to evaluate the beneficial effects of BCG vaccination at a population level of high risk health care workers through a mitigated clinical course of SARS-CoV-2 infection. The primary endpoint and the adaptive design with frequent interim analyses facilitate maximum efficiency of the trial, so that results can inform policy making during the ongoing epidemic.

1. INTRODUCTION AND RATIONALE

On 30 December 2019, a novel enveloped RNA betacoronavirus was detected from a patient with pneumonia of unknown etiology in Wuhan, the capital city of Hubei province. The pathogen was named the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). [1,2] Since beginning of 2020, SARS-CoV-2 spread rapidly throughout China and the rest of the world, the first detected case in the Netherlands on 27 February 2020. In the United States, there have been over 156,000 cases as of 30 March 2019.

From a cohort of patients with SARS-CoV-2 admitted to hospitals in the Wuhan region, (n=1099), a mortality rate of 1.4% was observed, with an ICU admission rate of 5% and 2.3% undergoing invasive mechanical ventilation.[2]

The estimated basic reproduction number (R0) of SARS-CoV-2 is ~2.2-2.7 and, on average, each infected person spreads the infection to an additional two persons. SARS-CoV-2 is being transmitted via droplets and fomites during close unprotected contact between an infector and infectee.[1] According to WHO, as of 20 February 2020, 75,465 laboratory-confirmed SARS-CoV-2 cases were established. Health-care workers face an elevated risk of exposure to- and infection of- SARS-CoV-2, although in China, surprisingly, infection of health care workers could mostly be traced back to in-household transmission.[3] Of these 75,465 laboratory-confirmed cases, 2,055 (2.7%) were reported among health care workers from 476 hospitals across China. The majority of cases (77.8%) were found in the working age (30–69 years).[1]

In Wuhan, the hospital admission of SARS-CoV-2 infected patients substantially outweighed the number of physicians, leading to unsafe care and in-hospital transmission.[4] Consequently, in the district of Wuhan 40,000 health care workers have been deployed from other areas of China to support the response in Wuhan.

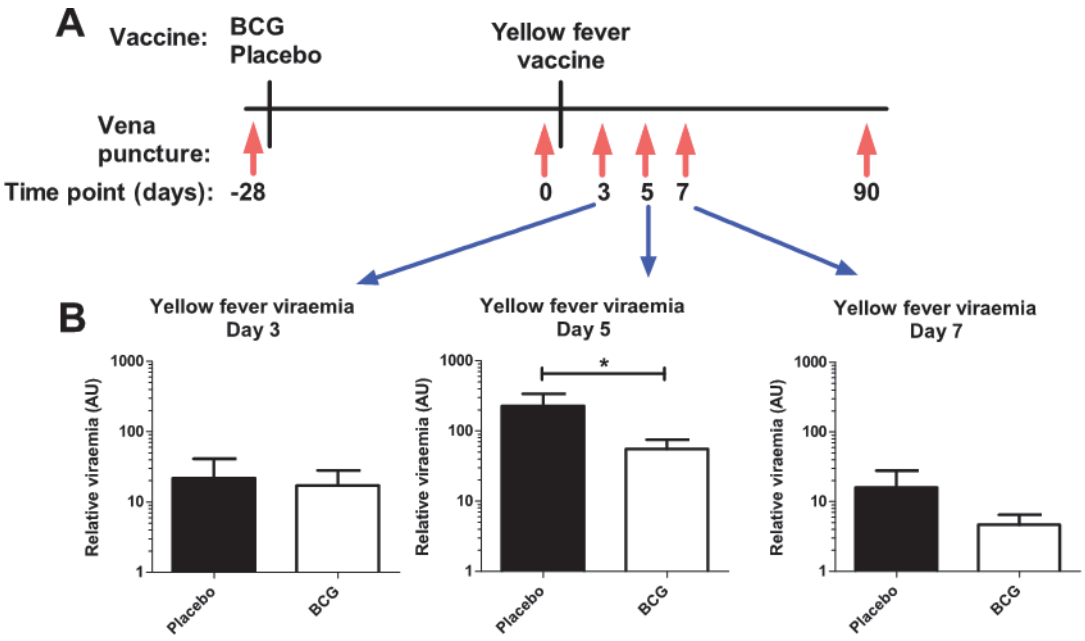
Subsequently, a SARS-CoV-2 pandemic reflects a serious threat to hospital personnel capacity, as the number of SARS-CoV-2 infected patients that require hospital care may well exceed the capacity of hospital personnel. It is imperative to ensure the safety, health and fitness of existing hospital personnel in order to safeguard continuous patient care. Strategies to improve the clinical course of SARS-CoV-2 infection are therefore desperately needed. To date, treatment for SARS-CoV-2 has been supportive, and no curative or protective treatments have been identified yet.

Bacillus Calmette-Guérin (BCG) was developed as a vaccine against tuberculosis, but many studies have shown its ability to induce potent protection against other infectious diseases: the so called non-specific effects (NSEs).[5] Moreover, BCG has non-specific clinical protective effects: early administration of BCG vaccination leads to reduced child mortality, mainly as a result of reduced neonatal sepsis, respiratory infections, and fever.[6–8] NSEs of BCG are not limited to children, as a recent study in adolescents has shown a 70% decrease in the incidence of respiratory tract infections in individuals vaccinated with BCG compared to placebo.[9] In addition, a small Indonesian trial has shown that consecutive BCG vaccination for 3 months reduced the incidence

of acute upper tract respiratory infections by 80% (95%CI=22-95%).[10] The non-specific beneficial effects of BCG are not restricted to infections, as BCG has also been used in patients with bladder cancer, to induce an improved reaction of the immune system, which prevents tumor progression and mortality.[11]

It has been recently demonstrated that the non-specific beneficial effects of BCG vaccination are due to epigenetic and metabolic reprogramming of innate immune cells such as myeloid cells and NK cells, leading to an increased antimicrobial activity, a process termed 'trained immunity'.[12] Upon stimulation with a pathogen, the innate immune system becomes primed and is able to react faster and more efficient to a secondary (and non-related) stimulus. In experimental studies, BCG has been shown to protect not only bacterial and fungal infections, but against viral infections such as influenza as well.[13] Furthermore, among humans receiving yellow fever vaccine virus, those who had received BCG had less viremia, and improved anti-viral responses compared to placebo treated subjects (Figure 1).[14] The observed effects are proposed to be due to modulation of the human innate immune system through 'trained immunity' and are long-lasting for at least one year[11,12].

Figure 1. A. Healthy volunteers were immunized with either placebo (n=15) or BCG (n=15). One month later all volunteers were injected with yellow fever vaccine. B. Viremia was assessed on day 3, 5 and 7 after yellow fever vaccination by PCR in the blood. BCG vaccination significantly decreased the viremia in the circulation.[14]



Based on the capacity of BCG to: i. reduce the incidence of respiratory tract infections in children and adults; ii. exert antiviral effects in experimental models; and iii. reduce viremia in an experimental human model of viral infection, we hypothesize that BCG vaccination may induce (partial) protection against susceptibility to and/or severity of SARS-CoV-2 infection. This study

will evaluate the efficacy of BCG to prevent and improve the clinical course of SARS-CoV-2 infection.

BCG vaccine in immunocompetent adult people is considered safe, even in latently infected adults with prior infant BCG vaccination.[15,16] In a randomized controlled trial that compared revaccination with BCG versus placebo, no serious adverse events were observed in the BCG arm.[9]

Additionally, we have analyzed data and found that over the 15-day period from 9 March to 24 March 2020, the incidence of Covid-19 was 80 per million population, with a fatality of 0.55 per million. A total of 178 countries were in the database: current national programs of BCG vaccination exist in 131 countries; 21 countries have no current program of national BCG vaccination; and for 26 countries status is unknown. When we dichotomised the data according to those countries with and without BCG programs, the incidence of Covid-19 was 38.4 per million in countries with BCG vaccination whereas the incidence of Covid-19 was 358.4 per million in the absence of such a program. Likewise, the fatality recorded in countries with BCG programs was 4.28/million, compared to 40/million in countries without a national program. Calculating a crude case fatality rate (CFR) by dividing deaths by cases, countries with a BCG program the CFR was 0.13% and 0.33% in countries without a BCG program. Countries that have a booster injection of BCG 7 to 14 years later had no better outcomes than those with a single inoculation only[1].

A randomized controlled trial provides the highest validity for this research question. Given the immediate threat of the SARS-CoV-2 epidemic the trial has been designed as a pragmatic study with a highly feasible primary endpoint, that can be continuously (e.g. symptoms continuously and serology every other week) measured. This allows for the most rapid identification of a beneficial outcome that would allow other HCWs (including the control population) to also benefit from the intervention if and as soon as it has been demonstrated to be effective.

2. RESEARCH QUESTIONS

Primary Objective:

1. To measure the efficacy of BCG vaccination among HCW in preventing infection with SARS-CoV2 in the United States.

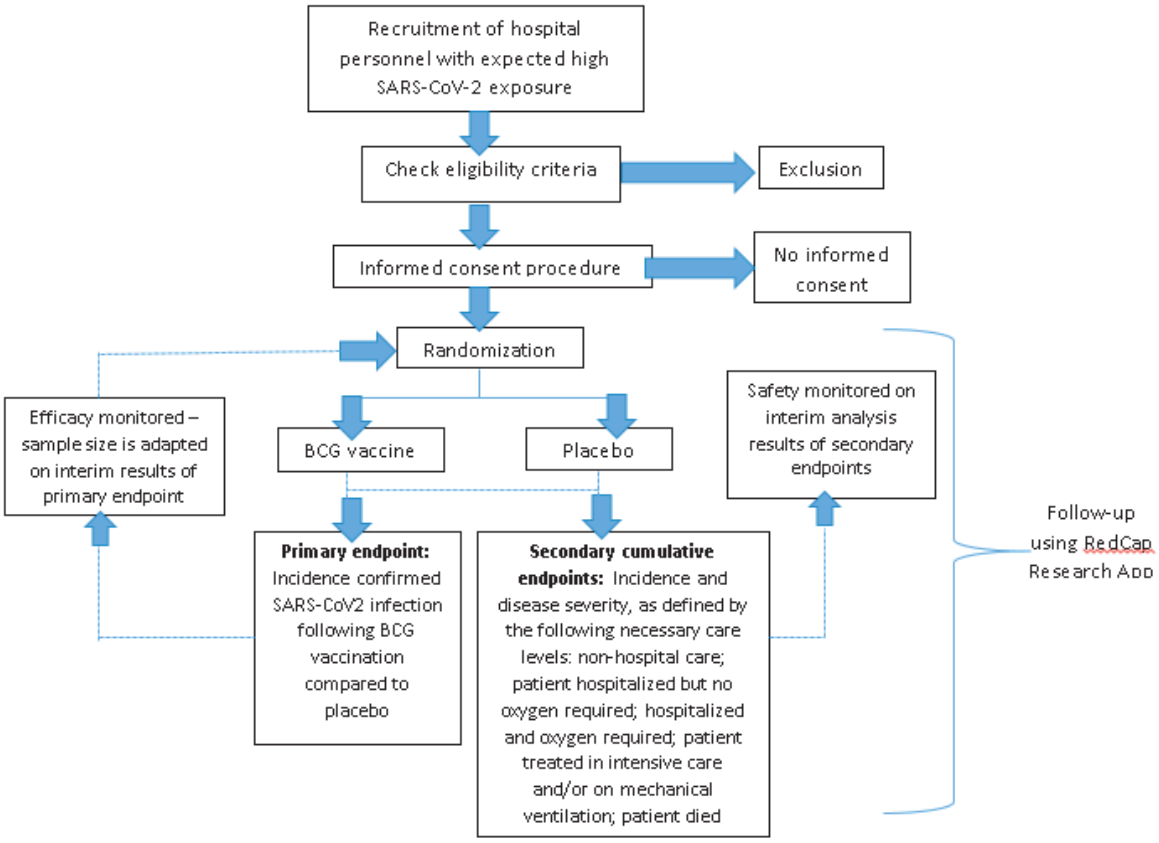
Secondary Objective:

1. To measure the efficacy of BCG vaccination among HCW in mitigating the severity of Covid-19 disease in the United States.

3. STUDY DESIGN

A placebo-controlled adaptive multi-center adaptive randomized controlled trial, see figure 2 for the logistics of the study.

Figure 2: Study design of the BAD-AS trial



a. DURATION OF FOLLOW-UP

The duration of follow-up for each participant depends on the interim results of the primary endpoint and the probability of obtaining a result, with a maximum of 168 days. The end of the study is defined as the last patient's last registration in the mobile application. Healthcare workers (HCWs) will collect fingerstick dried blood spot (DBS) samples for serology testing at baseline, weeks 4, 8, 12, 16, 20 and 24. If they develop symptoms, they will be qPCR tested by nasopharyngeal swab, oral swab and/ or fecal swabs.

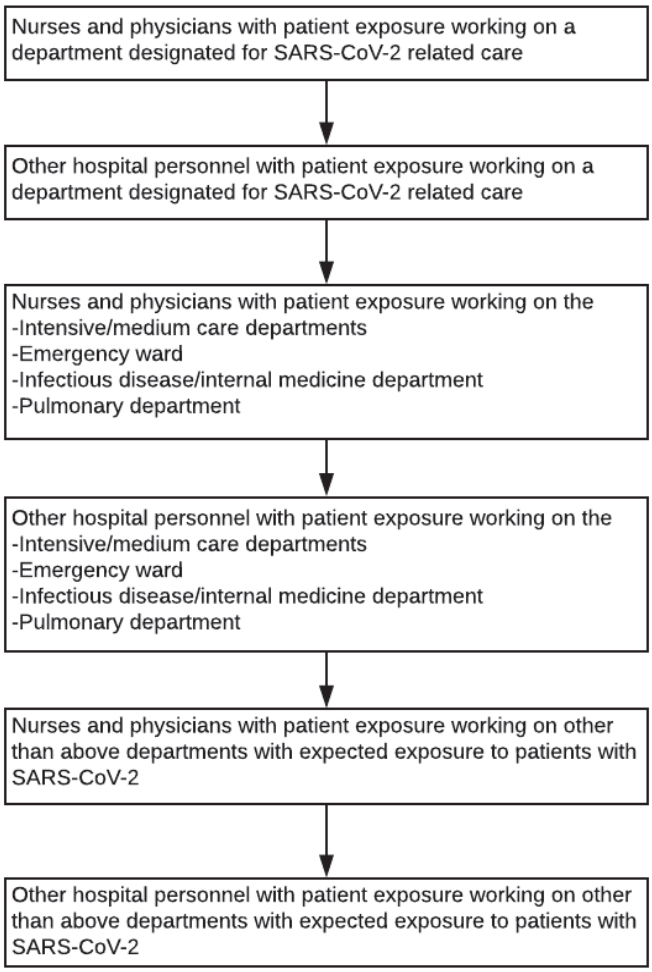
4. STUDY POPULATION

a. Population (base)

BCG vaccination 2 to 4 weeks before exposure to SARS-CoV-2 would lead to an optimal immunologic response and best expected clinical effects. As this time point cannot be determined (and may have already passed), participating hospitals will be selected by the study team based on their capability to perform study-related procedures. Currently, rapid tests to evaluate participants previous exposure to COVID19 do not exist, but will emerge in the coming weeks. Blood will be obtained and banked, and serologic status will be evaluated retrospectively.

In-hospital recruitment of hospital personnel will be done in different phases. The selection is based on the likelihood of taking care for patients with SARS-CoV-2 infection and, thus, the risk of SARS-CoV-2 exposure, see figure 3 for an example of recruitment.

Figure 3: Recruitment of subjects for the BAD-AS trial:



b. Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:

- Adult (≥18 years)
- Male or female
- Hospital personnel taking care for patients with known or suspected SARS-CoV-2 infection and providing, on average, at least 25 hours per week of direct patient care.

c. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Known allergy to (components of) the BCG vaccine or serious adverse events to prior BCG administration
- Known active or latent *Mycobacterium tuberculosis* or with another mycobacterial species. A history with- or a suspicion of *M. tuberculosis* infection.
- Fever (>38 C) within the past 24 hours
- Age > 75 years
- Pregnancy or planning pregnancy within 30 days of study enrollment
- Breastfeeding
- Suspicion of active viral or bacterial infection
- Any Immunocompromised subjects. This exclusion category comprises: a) subjects with known infection by the human immunodeficiency virus (HIV-1); b) subjects with known neutropenic with less than 1500 neutrophils/mm3; c) subjects with solid organ transplantation; d) subjects with bone marrow transplantation; e) subjects under chemotherapy; f) subjects with primary immunodeficiency; g) known severe lymphopenia with less than 400 lymphocytes/mm3; h) treatment with any anti-cytokine therapies. i) treatment with oral or intravenous steroids defined as daily doses of 10mg prednisone or equivalent for longer than 3 months
- Living with someone who is immunosuppressed or taking immunosuppressive drugs
- Previous documented infection with COVID19
- Active solid or non-solid malignancy or lymphoma within the prior two years
- Direct involvement in the design or the execution of the BAD-AS study
- Expected absence from work of ≥4 of the following 12 weeks due to any reason (holidays, maternity leave, retirement, planned surgery etc)
- Not in possession of a smartphone
- Inability to keep the vaccine site covered in the case of a draining pustule.

Secondary analysis: Disease severity will be based on the level of care required for individuals who test positive for COVID19 as follows: non-hospital-based care; patient hospitalized but no oxygen required; hospitalized and oxygen required; patient treated in intensive care and/or on mechanical ventilation; patient died. Additional WHO criteria for severity include severe pneumonia, respiratory failure, acute respiratory distress syndrome, sepsis and septic shock. Days absent will be self-reported via the CRF. Immunology and epigenetic studies for innate training be

implemented as previous discussed[2-5], but in brief, immune cells will be stimulated with non-specific (LPS, mitogen, BCG) and COVID19-specific antigens with immune function measured by ELISA and flow cytometry. Epigenetic studies are discussed in more below.

d. Coordination among participating sites

This is a multi-site study with Houston (BCM, MD Anderson and TAMU) and Boston (Harvard) starting enrollment. Other sites may participate in the United States, but will obtain their own local IRB approval to do so along with executing data use agreements.

The general study design was originally developed by Dr. Mihai Netea from Radbound, Netherlands. They are implementing a similar study using slightly different primary and secondary outcomes and a different strain of BCG. In addition, Dr. Nigel Curtis has already started a 4,000 HCW study in Australia measuring similar clinical outcomes. The PIs of this study will coordinate safety and efficacy with those collaborators, however the data from the United States will be analyzed independently.

All sites will use the same electronic data capture form (RedCap), the same data dictionaries and the same data management plans. Each institution will use independent RedCap "instances" and de-identified data will monthly be exported and be analyzed by the DSMB.

5. TREATMENT OF SUBJECTS

a. Investigational product/treatment

In the United States, only the FDA approved TICE® BCG (for intravesical use) BCG LIVE strain of the BCG (Merck) vaccine or a saline placebo will be administered. This will be given intradermally (0.1mL) in the deltoid area. We are NOT using the BCG Vaccine USP which is also the Tice strain of BCG as it is indicated for the prevention of *Mycobacterium bovis*, at a different dose, following a different preparation and by means of a different route of administration.

In Houston, randomization will also occur 1:1. (Block randomization discussed below) Placebo vaccine will be 0.1 mL 0.9% NaCl, which is the same amount and color as the intervention.

We remain open to guidance from the FDA and IRBs regarding utilizing additional strains of BCG (eg Russian Strain (Verity), Tokyo Strain (JBL), as they might become available and as necessary). However, we confirm that no other forms of BCG will be administered without IRB and FDA approval. As of 3 April 2020, only the BCG Tice strain will be used in the United States.

6. INVESTIGATIONAL PRODUCT

a. Name and description of investigational product(s)

Participants that are randomized in the active arm will receive BCG vaccine, the FDA-approved TICE® BCG (for intravesical use) BCG LIVE strain in the United States.

b. Summary of findings from non-clinical studies

BCG has been shown to have the ability to train the innate immune system in an in vitro and in vivo setting. eg. when human monocytes are incubated for 24h in vitro with BCG and after a week are re-challenged with another (part of a) pathogen, the cytokine

production is increased, compared to non-BCG trained monocytes. [17] BCG also protects in experimental models of viral infections (e.g. influenza) in murine models. [13]

c. Summary of findings from clinical studies

BCG vaccine has been shown to induce training of the innate immune system in vivo, just as heterologous effects of the adaptive immune system (e.g. increased cytokine production by monocytes and lymphocytes of BCG-vaccinated individuals), which is thought to have a protective effect in countries with a high infectious pressure (e.g. most third world countries).[17,18] After vaccination with BCG, immune cells isolated from healthy individuals react with an increased production of proinflammatory cytokines after stimulation with both specific (MTB) and non-specific (bacterial, viral, fungal) stimuli. Adolescents vaccinated with BCG have shown a 70% decrease in the incidence of respiratory tract infections compared to placebo[9]. In a small Indonesian trial, consecutive BCG vaccination for 3 months reduced the incidence of acute upper tract respiratory infections by 80% (95%CI=22-95%). [10]

d. Summary of known and potential risks and benefits

The potential benefit for subjects randomized to the BCG-arm is that administration of the vaccine could prevention SARS-CoV-2 infection and lower risk on developing severe illness caused by SARS-CoV-2.

Potential risks include only the well-known side effects of both the vaccines. A short summary of the most common side effects includes: discomfort at the injection side, scarring at injection side, fevers, nausea, vomiting. Severe but very uncommon side effects are: neurological symptoms such as injection site abscesses, BCG lymphadenitis, disseminated BCG diseases, osteitis, osteomyelitis, anaphylaxis, formation of keloid/lupoid, suppurative lymphadenitis. A complete list of known side effects can be found in the information product insert.

Subjects that receive the placebo hardly have any potential risks and no benefits. Local hematoma formation can occur at the site of vena puncture.

e. Route of administration and dosage

The TICE® BCG (for intravesical use) BCG LIVE strain will be administered in the upper arm slowly (deltoid area), in about 10 seconds, intradermally 0.1ml of the suspended vaccine, which accounts for approximately 0.075mg of attenuated *Mycobacterium bovis*. The administered 0.1 mL of reconstituted TICE® BCG (for intravesical use) BCG LIVE strain vaccine is approximately $2x10^5$ CFU.

Placebo: Administer at the left upper arm slowly, in about 10 seconds, intradermally 0.1ml of 0.9% NaCl solution.

g. Preparation and labelling of Investigational Product (IP)

Preparation and labelling of the investigational products are performed according to GMP guidelines.

In the United States, ICE® BCG (for intravesical use) BCG LIVE strain will be purchased from Merck and reconstituted and prepared according to the package insert/per the approved prescribing information and will include:

a) preparation using aseptic technique during reconstitution as stipulated in the prescribing information for TICE BCG (for intravesical use) BCG Live.

b) that reconstituted TICE® BCG should be kept refrigerated (2–8°C), protected from exposure to direct sunlight, and used within 2 hours of reconstitution.

c) Unused solution should be discarded after 2 hours.
d) Intact vials (prior to reconstitution) of TICE BCG should be stored refrigerated, at 2–8°C (36–46°F).

Merck sells and distributes $1x10^8$ CFU of TICE® BCG (for intravesical use) BCG LIVE strain in a lyophilized (freeze-dried) powder and this will be reconstituted in 50 mL of preservative-free saline, yielding $2x10^6$ CFU/ mL. Administration of 0.1 mL will contain ~$2x10^5$ CFU, similar to the quantity of BCG vaccine administered worldwide.

The TICE® BCG (for intravesical use) BCG LIVE strain format of the BCG vaccine available in the United States comes in quantities of $1x10^8$ CFU per vial and must be used within 2 hours of reconstitution).

h. Drug accountability
Drug accountability will be done in compliance with each pharmacy per their local standard operating procedures and institutional requirements and dispensed from each local pharmacy's supply.

7. STUDY PARAMETERS/ENDPOINTS

a. Primary study endpoint
Incidence of rt-PCR-confirmed SARS-CoV2 infection following BCG vaccination compared to that following placebo.

b. Secondary study endpoint
In individuals who test positive for Covid-19, the proportion with severe disease following BCG vaccination compared to placebo, as defined by the following necessary care levels: non-hospital care; patient hospitalized but no oxygen required; hospitalized and oxygen required; patient treated in intensive care and/or on mechanical ventilation; patient died.

8. STUDY PROCEDURES

a. Recruitment, Randomization, treatment allocation, and blinding
A standardized, IRB approved email will be sent to department chairs describing the study. A research coordinator will reach out to interested participants via phone with the help of

an IRB-approved verbal script to introduce the study, confirm eligibility and provide further instructions on how to access and sign the IRB-approved ICD via REDCap using their own electronic devices. It is important that we obtain the consent via REDCAp to a) avoid direct person-to-person contact and comply with social distancing imposed recommendations, and b) minimize the waste of reconstituted BCG by allowing the research personnel to schedule vaccinations in a controlled fashion. Patient registration into the trial will happen immediately after consent has been provided and will involve entering of baseline information into an electronic data capture system (RedCap).

Once the eligibility is confirmed and the ICD signed by the participant and stored in REDCap, the research coordinator will randomize the participant and communicate the treatment assignment to the nurse administering the vaccination. The nurse will subsequently assign an appointment and communicate date and time of vaccination with the participant. All eligible participants will receive intradermal injections of BCG:placebo in a 1:1 ratio.

Both, participants and investigators will be blinded to the treatment assignments during the study. However, in case of an emergency where it is important to know the treatment received, the investigator and/or participant can reach out to the unblinded study personnel who will provide the unblinded data. All participants will receive their treatment allocation at the end of the study, after the data analysis is finalized.

Unblinded personnel will not be involved in the collection and analysis of study data other than the baseline eligibility criteria.

The end of the study is defined as the last patient's last entry in the electronic data capture system.

b. Informed Consent and Eligibility

The following types of procedures will be conducted as indicated below:

Medical **history** will be obtained from patient medical record/clinical chart. Informed Consent will be obtained to access these records. When information cannot be obtained or is not available from the patient medical record/clinical chart, it will be obtained via patient interview.
Physical **examination** will be conducted solely to look for existing BCG vaccination scars.

Symptom **evaluation** will be conducted via an electronic survey administered to participants every 1-3 days.

HIV **and pregnancy** will be collected as self-reported information. If unknown, a urine pregnancy test will be performed.

Nasopharyngeal, oral and/ or rectal **swabs** will be collected for rt-PCR test for SARS-CoV2 infection if a study develops symptoms consistent with Covid-19.

If a participant does not know their PPD/IGRA status from within the last 24 months (all health care providers should have this information), an IGRA can be performed to evaluate eligibility.

Study participants have the option of donating blood via phlebotomy (for serological test for Covid-19 disease and PBMCs for immune correlates) or providing a fingerstick and dried blood spot (for serologic test for Covid-19).

Data will be collected at four time points/periods: (1) after consent, (2) at baseline, (3) during follow-up period, and (4) at study end.

Data to be collected during screening includes medical history, physical exam results, results of rt-PCR and serological test results.

Data to be collected during baseline enrollment includes eligibility confirmation, demographic information, risk factors, randomization assignment, confirmation of BCG vaccination/placebo, any immediate reactions to BCG vaccination/placebo.

Data to be collected during follow-up includes intermittent surveys about the presence of flu-like symptoms, rt-PCR test results if done, serological test results, if testing positive for Covid-19 information regarding their disease course, and disease outcome status.

The following procedures will be performed and/or data collected as listed below data after informed consent is obtained:

Data Variable	
Date of signed Informed Consent Form	X
Role in hospital	X
Department in hospital	X
rt-PCR test for SARS-CoV2 result	X
Serological test for Covid-19 result	X
Number of BCG scars (by visual/physical examination)	X
Medical history*	X
Previous PPD and IGRA test results	X
History of TB disease	X
History of previous HIV testing	X
Urine Pregnancy test result (if applicable)	X
Plans of pregnancy in 30 days	X
Plan to stop working in 3 months/ leave facility in 6 months	X
Current diabetes mellitus	X
Current chronic kidney disease	X
Currently taking immunosuppressive drugs	X
Living with someone with HIV, immunocompromised, taking immunosuppressive drug	X
Chemotherapy in past 3 months	X

History of organ/bone marrow transplant	X
Access to smartphone	X

c. Baseline data collection/procedures

The following procedures will be conducted and data collected as indicated below:

A questionnaire to obtain information about age, sex, demographic information, who they live with, smoking status, any current medications they are on, and other comorbidities

Participants will then be randomized to either receive a single dose of BCG vaccination or placebo.

BCG vaccination or placebo will be administered.

Eligibility screening data will carry forward into the trial.

The following additional data points will be collected:

Data Variable	
Age	X
Sex	X
Race	X
Ethnicity	X
Nationality	X
Who they live with	X
Height	X
Weight	X
Smoking status/tobacco use	X
Alcohol use	X
Current list of medications	X
Current list of comorbidities	X
History of diabetes mellitus	X
History of hypertension	X
History of stroke	X
History of kidney disease	X
History of COPD	X
Randomization assignment	X
BCG/placebo administered	X

d. Follow-up procedures and data collection:

Participants will be followed to assess whether they get infected with SARS-CoV2:

Participants will complete intermittent surveys via an electronic system every 1-3 days to assess the presence of any flu-like symptom, including sore throat, fever, headache, malaise, and cough. Note that this is part of routine surveillance for Covid-19 in health workers at the United States site. Consent forms will ask for consent to access this survey information.

Any positive response on the survey will trigger a nasopharyngeal, oral and/ or rectal swab to be collected to test for Covid-19 via rt-PCR

All participants, regardless of survey responses, will have serology for Covid-19 tested at 4 week intervals during the follow-up period (6 months)

If a participant completes the follow-up period and does not test positive for disease, their study participation is complete

If a participant does test positive for disease, their disease status will be ascertained for up to two months or until an outcome is available through one of the following mechanisms: (1) an electronic survey if they are not admitted to the hospital, including questions about the number of days they are ill, daily fever, and other symptoms; or (2) (2) if they are admitted to the hospital, ordinal outcomes for disease severity will be extracted from the hospital's electronic medical records system.

During the first week of follow-up, all participants will actively be asked about any adverse events; thereafter, participants will report unsolicited AEs through the electronic survey. Vaccine related adverse events will be graded using the FDA guidance (https://www.fda.gov/media/73679/download) and noted using WHO-recommended Adverse event following Immunization forms (AEFI; https://vaccine-safety-training.org/classification-of-aefis.html).

Participants will have the option of donating 12 mL of blood for plasma (serology) and PBMCs for secondary analysis of immune correlates and for future analysis based on covid19-specific IgM and IgG. If they do not donate 12mL of blood, a fingerstick will be required for baseline COVID19 serology.

Dried Blood Spot (DBS): all participants are HCWs and will self-collect DBS samples at week 4, 8, 12, 16, 20 and 24. Envelopes to store the DBS are provided upon enrollment and can be dropped off at work and picked up by study coordinators to minimize HCW distractions.

COVID specific RNA is found in stool for ~21 days when an individual develops infection (https://doi.org/10.1038/s41586-020-2196-x). Participants will have the option of collecting stool swabs monthly if they are asymptomatic or weekly if they develop symptoms. Nucleic acid testing will be performed in retrospect to support secondary objectives.

If participants develop symptoms consistent with COVD19, will be PCR tested for COVID19. They will be given the option of donating 12 mL of blood for plasma and PBMCs 2 weeks after symptoms resolve.

Week 12 (+/- 2 Weeks), participants will be given the option to donate 12 mL of blood for plasma and PBMCs for secondary analysis of immune correlates and for future secondary analysis based on covid-specific IgM and IgG.

Week 24 (+/- 2 Weeks), participants will be given the option to donate 12 mL of blood for plasma and

PBMCs for secondary analysis of immune correlates and for future secondary analysis based on covid-specific IgM and IgG.

Except for the administration of BCG vaccine or placebo and the above mentioned DBS and phlebotomy, participants will undergo no invasive procedures for study purposes.

The following data points will be collected during the follow-up period and at end of study:

Data Variable	
Sore throat (collected at multiple time points)	X*
Fever (collected at multiple time points)	X*
Headache (collected at multiple time points)	X*
Malaise (collected at multiple time points)	X*
Cough (collected at multiple time points)	X*
rt-PCR test for SARS-CoV2 result (as indicated)	X
Serological test for Covid-19 result (every 2 weeks)	X
Number of days ill	X
Daily fever	X
Other Covid-19 symptoms	X
Admitted to hospital	X
Required oxygen	X
Treated in intensive care	X
Required ventilation	X
Death	X
Severe pneumonia	X
Respiratory failure	X
Acute respiratory distress syndrome	X
Sepsis	X
Septic shock	X

**Already being collected as part of routine surveillance of health care workers. Will request access to this information in Informed Consent Form.*

e. Withdrawal of individual subjects/End of Study

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Participants who received placebo will be unblinded at the end of the study and pending a recommendation by the DSMB, they will be offered the option of receiving the BCG intervention.

f. Replacement of individual subjects after withdrawal

A participant will only be replaced in case of withdrawal before the administration of BCG vaccine/placebo.

g. Premature termination of the study

During the study, frequent interim analyses will be planned. The safety and futility of the trial will be monitored carefully by the study team and DSMB during these interim analyses. If warranted, the study will be terminated (prematurely). Description of the DSMB and interim analysis is described further below.

9. SAFETY REPORTING

a. Temporary halt for reasons of subject safety

The investigators will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The investigator will notify the IRB without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the IRB. The investigator ensure that all subjects are kept informed.

b. AEs, SAEs and SUSARs

i. Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product, the placebo or the trial procedures. Adverse events can be self-reported by the subjects using the mobile application. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded and assessed per institutional IRB and policies.

ii. Expected mild Adverse events

Although BCG vaccination almost always causes local reactions, serious or long-term complications are rare. Almost all recipients of BCG will experience vaccine site erythema and development of a small pustule. Slight tenderness at the puncture site may be encountered as well as some itching. The initial skin lesions usually appear within 10–14 days and consist of small red papules at the site. The papules reach maximum diameter (about 3 mm) after 3 to 4 weeks, after which they may scale and then slowly subside.

Theoretically it is feasible that a HCW BCG vaccinated could shed attenuated live BCG and transmit this to an immunocompromised patient. While theoretically feasible, we found no case reports of such events. Further, the ability to keep the vaccine site covered is an exclusion criterion. Study participants will be notified of the expected pustule formation and the need to keep it covered by gauze and clothes during the period it is draining. Before the pustule drains, it has characteristic fluctuant appearance and should be covered with gauze from the time fluctuance develops.

iii. Expected rare, serious Adverse events:

Approximately 1 in 1000 to 1 in 10,000 will experience suppurative lymphadenopathy including moderate axillary or cervical lymphadenopathy and induration and subsequent large pustule formation \. While local usually resolved within 3-4 weeks, supportive lymphadenopathy can persist for as long as 3-6 months after vaccination. There is not definitive management for suppurative lymphadenitis and treatment will be managed on a case by case basis with some undergoing "watchful surveillance and others drained with incision and drainage. All adverse events will be discussed by the site and overall PIs.

More serious local reactions include ulceration at the vaccination site, regional suppurative lymphadenitis with draining sinuses, and caseous lesions or purulent draining at the puncture site. These manifestations might occur up to 5 months after vaccination and could persist for several weeks. The intensity and duration of the local reaction depends on the depth of penetration of the multiple puncture device and individual variations in patients' tissue reactions.

The most serious complication of BCG vaccination is disseminated BCG infection. The most frequent disseminated infection is BCG osteomyelitis (0.01 to 43 cases per million doses of vaccine administered) which usually occurs 4 months to 2 years after vaccination. Fatal disseminated BCG infection has occurred at a rate of 0.06–1.56 cases per million doses; these deaths occurred primarily among immunocompromised persons. Disseminated BCG will be treated and managed by each site PI and treated with antibiotics (rifampicin, isoniazid, ethambutol). The risk of anaphylaxis to BCG has been described but is very rare. In a study of over 50,000 individuals who received BCG or placebo, anaphylaxis occurred in no individuals receiving BCG (PMID8691924). The vaccination will take place within 0.5 mile of a hospital in the event this occurs. There is nowhere in the TMC area that would not therefore be suitable.

Theoretically, it is feasible that BCG could induce an enhanced innate immune response that induces exuberant immune pathology when an individual is secondarily infected with covid19. Existing human and animal models suggest that BCG will improve antiviral immunity and not induce immunopathology. A recent report in the Lancet suggests that covid related disease is due to suppressed immunity, not due to exuberant immunopathology (Wang To et al https://doi.org/10.1016/S1473-3099(20)30196-1 Chen and Li, Lancet ID: https://doi.org/10.1016/S1473-3099(20)30235-8), but high viral load and lack of host immunity. Participants will be completing daily symptom dairies and results will be reviewed every 4 weeks by a DSMB consisting of immunology, pulmonology, and infectious disease physicians. In personal correspondence from Dr. Lamm (letter available upon request), he reports anecdotal evidence that BCG does not induce an increase in viral infections. Further, in the ACTIVATE trial, which took place this past year, 200 elderly patients in Greece upon hospital discharge received either BCG vaccination or placebo. None have since developed a covid-related ARDS response (letter from Dr. Kanellakopoulou and email from Dr. Netea available upon request.)

iv. Serious adverse events (SAEs)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB per their policy and institutional guidelines .

v. Suspected unexpected serious adverse reactions (SUSARs) / Unanticipated Problems (UP)

- UPs are defined according to each institutional IRB of record. The UP will be defined and reported per institutional policy. All serious adverse events will be reported to local site PI within 24 hours of knowledge of the event.
- Unless stated otherwise in the protocol, all SAEs, expected or unexpected, will be reported to the DSMB as soon as possible, but in all cases within 5 working days of knowledge of the event regardless of the attribution.

- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported within 24 hours of knowledge of the event.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, unless the protocol states otherwise, and be reported until 30 days after the last protocol specific data collection timepoint. Serious adverse events must be followed until clinical recovery is complete and standard of care laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period, or protocol specific timeline, that are related to the study treatment must be reported to the IRB Office.

c. Data Safety Monitoring Board

Safety oversight will be provided by a DSMB. The DSMB consists of 5-7 expert members and are independent of study personnel. The DSMB will consist of members with expertise related to the trial. The DSMB will be run via teleconference with representatives from both Boston and Houston including the following current members. Dr. Daniel Musher (infectious disease physician, BCM), Dr. Naval Daver (oncologist and immunotherapy expert, MD Anderson), Prof. Michael Hughes (senior biostatistician, Harvard School of Public Health), Dr. Martin Hirsch (infectious disease physician Massachusetts General Hospital), Dr. James Maguire (infectious disease physician Brigham and Women's Hospital) and Dr. Guilherme Godoy, (bladder cancer oncologist, BCM), and Dr. Edward Graviss, an expert in mycobacterial infections and statistical design and evaluation. If these existing members are unable to participate, they will be replaced with another member with similar expertise. The DSMB will review study collected data and events every month including enrollment, demographics, compliance, adverse events. The DSMB can also meet ad hoc in the event of an unanticipated SAE. The DSMB statistician, currently Dr Graviss, will have access to unblinded study data to evaluate these criteria. A final data review meeting will occur two to four months after study completion to review the cumulative safety data. Additional data can be requested by the DSMB as they deem requisite. The DSMB may share de-identified reports with participating/collaborating sites and/or institutions.

d. Halting Rules

The DSMB or study PI may halt the study in for the following reasons:

- Two or more participants develop anaphylaxis
- Three or more participants develop disseminated BCG or suppurative lymphadenitis
- Three or more participants develop disseminated BCG-itis
- Any participant experiences a serious unexpected adverse event that could be related to vaccination
- A 5% increase in severe COVID19 related illness (severe pneumonia, respiratory failure, ARDS, sepsis, septic shock) among those vaccinated compared to those that received placebo

e. Annual safety report

In addition to the expedited reporting of SUSARs, the Investigator will submit, a summary of safety reports to their IRB, annually, per their local policy and institutional guidelines..

f. Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs collection and reporting will occur until end of study, as defined in the protocol.

10. SAMPLE SIZE AND STATISTICAL ANALYSIS

Data will be reported quantitatively. All analyses will be performed from the intention-to-treat principle. Missing data will be dealt with by multiple imputation using the mice package in R.

a. Sample size calculation

The study in the United States will include at least two sites (BCM and MD Anderson Cancer Center, Houston considered as 'one site' due to proximity) and Harvard Medical Center, Boston as the second site) with each site enrolling 350 individuals. The proposed enrollment sample size is designed to provide 80% power to detect a 60% vaccine efficacy (a relative risk of 0.4 among the vaccinated). This is based off the observed three-fold decline in respiratory infections in the South Africa adolescent cohort) with 80% power and 0.005 type-1error in a two-tailed test. We expect 10% of HCWs to develop symptomatic COVID19 during follow-up, therefore a sample size of 700, with 350 receiving intervention and 350 receiving placebo. We do not expect significant lost to follow up among HCWs. We will plot Kaplan-Meier curves comparing COVID19 disease between the BCG and placebo groups and report hazard ratios and p-values using Cox proportional hazard models. DBS samples will be collected at baseline and weeks 4, 8, 12, 16, 20 and 24 post intervention. PBMCs and plasma donations are optional at baseline, 12 and 24 weeks, but considering this is a HCW study, we hypothesis donations will be at least 50%. Interim analysis will occur at weeks 4, 8, 12, 16, 20 and 24 and will be reported to the DSMB. If interim analysis identifies a large proportion of participants to be seropositive before intervention, power analysis will be re-evaluated and an amendment will be submitted.

b. Interim analysis

Every month, an interim analysis will be held by the independent statisticians of the trial (will occur first independently in Boston and Houston and then data collated and merged). The above described statistical analysis will be evaluated as well as safety profile. In the United States, we will perform five interim analyses at 4-, 8-, 12-, 16-week follow-up and then one final analysis. To maintain the overall type-1 error =0.05, the type-1 errors at 4-, 8-, 12-, 16-, 20- and 24- weeks follow-up are set to be 0.00000025, 0.0011, 0.0063, 0.0153, 0.0266, and 0.0388 respectively (O'Brien-Fleming boundary). We will stop the clinical trial early if the p-value of any interim analysis is smaller than the pre-specified type-1 error cutoff. Each interim analyses will be reported to the DSMB.

c. Primary study parameter(s)

The primary endpoint, development of COVID19 infection, we will use the Cox proportional-hazards model to calculate hazard ratios for the development of Covid-19. This will be reported as the proportion of individuals receiving the intervention who are PCR-positive or seroconvert.

d. Secondary study parameter(s)

Disease severity as discussed above and based on guidelines proposed by the World Health Organization. We will use the Chi square for significance to calculate the risk ratios for the development of severe Covid-19 disease. Disease severity will be based on the level of care required for individuals who test positive for COVID19 as follows: non-hospital-based care; patient hospitalized but no oxygen required; hospitalized and oxygen required; patient treated in intensive care and/or on mechanical ventilation; patient died. Additional WHO criteria for severity include severe pneumonia, respiratory failure, acute respiratory distress syndrome, sepsis and septic shock. Days absent will also be self-reported via the RedCap Research App. Immunology and epigenetic studies for innate training be implemented as previous discussed2-5, but in brief, immune cells will be stimulated with non-specific (LPS, mitogen, BCG) and COVID19-specific antigens with immune function measured by ELISA and flow cytometry. Epigenetic studies are discussed in more detail below.

e. Other study parameters

Continuous baseline characteristics will be reported as mean and standard deviation or median and inter-quartile range, as appropriate. Categorical baseline characteristics will be reported as count and percentage. No statistical testing for baseline characteristics will be performed.

f. Synthesis

In this trial, the BCG vaccine will be used in hospital personnel during the epidemics to prevent infection with the new SARS-CoV-2 virus. The risk of the BCG vaccine is very well known (see product inserts) and only minor local side effects (redness, local pain) are common. The benefits of BCG vaccination based on earlier clinical studies are expected to be a reduction in infection and morbidity of at least 25% compared to unvaccinated individuals, and potentially much higher. These effects are mediated by the capacity of BCG to induce trained immunity and may represent an important tool for protection against SARS-CoV-2 virus infection until a specific effective vaccine is developed.

g. Epigenetic and Immune Corollary Studies

COVID19 serology is currently being developed. When available (FDA approved test availability is rapidly evolving and improving), serology from blood drawn at baseline will be used to exclude individuals with preceding COVID19 infection from analysis.

To evaluate if the metabolic-epigenetic-immune mechanisms of the non-specific benefits of BCG for Covid19 are similar to that as previously described (Arts et al 2017), the collection of 12 mL of blood, in sodium heparin tubes, will be option to the participant. Blood will be processed for plasma (~4mL) and PBMCs. PBMCs will be cryopreserved and saved for future epigenetic (ATAC-seq, ChIP-seq, DNA methyl EPIC) and immune functional studies.

h. Flow cytometry based immune profiling

A secondary objective of this project is to elucidate the duration and immune correlate of protection of non-specific epigenetic-mediated immune "innate training" by BCG against Covid19. To do so, we will evaluate transcription regulation (DNA methylation, ATAC-seq, Chromatin immunoprecipitation), gene expression (reverse transcription PCR, RNA-seq) and immune phenotyping experiments (ELISAs) and multi-parameter immune phenotyping. We have developed multiple flow cytometry panels to measure the immune response. DNA methylation EPIC and other sequencing based arrays allow for genome wide evaluation of epigenetic silencing. Genome wide evaluation will be validated with site-specific evaluation using PCR as previously described (DiNardo et al JCI 2020; 32125282). Flow cytometry-based immune phenotyping allows 18 parameters to simultaneously be measured. By first stimulating the PBMCs with viral or mycobacterial peptides, we are able to simultaneously **measure and correlate** the quantity and quality of the viral and/ or mycobacterial induced immune phenotype (CD4, CD8, CD36, CD14, CD23), transcriptional changes (T-bet, GATA-3, Foxp3, Helios) and functional immune response such as cytokine release (IL-2, IL-4, IL-10, TGF-β, TNF and IFN-γ) or effector function (perforin, CD107a). COVID19-specific viral peptide mixes are in development and the PBMCs will be saved for a time when measuring COVID19-specific immunity is feasible.

i. Epigenomic DNA methylation

BCG induced non-specific immunity has been linked to chromatin conformation and DNA methylation. Therefore, these additional epigenetic studies will be evaluated as part of secondary analysis. The Illumina Infinium MethylEPIC array tests ~850,000 methylation sites including promoters, enhancers and non-island sites. Briefly, genomic DNA (gDNA) will be isolated (DNeasy protocol) from $1x10^6$ PBMCs with >80% viability. From this quantity of PBMCs, I am able to retrieve >1.5µg DNA, which is sufficient to implement this assay (500ng). Experiments only proceed after strict quality control analyzing nucleic acid quality using a Qubit 3.0 fluorometer and Agilent 4200 Tape Station System. I will use the Zymo EZ DNA Methylation kit to bisulfite treat 500ng of gDNA prior to MethylationEPIC testing. Methylation IDAT files will be imported into R statistical system using the Bioconductor (http://www.bioconductor.org) minfi package. After preprocessing and normalization, the Bioconductor limma package will identify probes with greater than 2 or less than 0.5-fold differential methylation with p-values < 0.05. Statistically significant differentially methylated probes will be visualized in Ingenuity Pathway Analysis. Gene ontology (GO) and Gene Set Enrichment Analysis analysis will be implemented using Molecular Signature Database (MSigDB) using hyper-geometric distribution that accounts for multiple comparisons. To evaluate if cell composition is confounding results and to determine the DNA methylation status of specific cell types (CD4, CD14, CD8, NK, and B cells), I will implement the bioinformatic pipelines EDEC (Epigenomic deconvolution) and MeDeCom (methylation decomposition). Both methods utilize linear algebra and classification techniques to quantify the DNA methylation profiles in several steps: 1) identifying optimal number of informative cell subpopulations 2) identify simultaneously both the estimated percentage of and the DNA methylation profile of each cell subpopulation. The explanatory cell subpopulations are then matched to DNA methylation profiles of known references via Spearman correlation. This approach offers multiple benefits: it enables us to assess DNA methylation changes in a cell

type specific manner, but in a cost-effective approach because I will be profiling only the heterogeneous blood cells. Validation of bioinformatic EDEC results will then be carried out in magnetic bead purified cell types as described below.

j. ATAC-seq

DNA hyper-methylation inversely correlates with chromatin accessibility, however other means of epigenetic silencing exists (i.e H3K27me3, etc.). Therefore to confirm that specific DNA hyper-methylation marks correlate with decreased chromatin accessibility, we will implement ATAC-seq, epigenome-wide chromatin accessibility evaluation. $1x10^5$ cells of interest (identified after EDEC as described above) undergo cell lysis, Tn5-mediated transposition followed by DNA purification, PCR amplification, DNA quality Bioanalysis (using Agilent and Qubit as described above) and sequencing. Bioconductor packages will be used for preprocessing, normalizing and identification of differential chromatin accessibility defined as greater than 2 or less than 0.5-fold difference with p values < 0.05.

k. Benefits and risks assessment, group relatedness

The risk to and burden for the subject of BCG vaccination is estimated to be low, according to two previous trials that have been performed with BCG vaccines. [9,10,14] The beneficial effect BCG vaccination for the individualized participant is unknown, although the objective is to prevent severe illness to SARS-CoV-2 infection. Using an adaptive design, the study aims to find a positive effect of BCG-vaccine on a population level, which could be applied quickly in participants allocated to placebo and implemented to hospitals that do not participate in the study.

11. STRUCTURED RISK ANALYSIS

a. Potential issues of concern

An extensive description of the mechanisms of action of the BCG vaccine, referring to the available in vitro and in vivo evidence, could be found in the Summary of Product Characteristics and the Product Insert.

a. Level of knowledge about mechanism of action

BCG activates NOD2 receptor pathway, and subsequently induces long-term epigenetic changes in chromatin of myeloid cells[12]. The epigenetic reprogramming leads to increased antimicrobial activity of myeloid cells (cytokine production, phagocytosis, reactive oxygen species release). At the same time, BCG induces potent activation of cellular specific immunity, with strong induction of Th1 responses and IFNg release. [14,17]

b. Previous exposure of human beings with the test product

In a randomized controlled trial, healthy volunteers were vaccinated with placebo or BCG (Baccillus Calmette Guérin) vaccine. These volunteers were injected 14 days latter a tri-valent influenza A vaccine. Volunteers previous vaccinated by BCG developed significantly greater titers against hemagglutinin A of the influenza A virus whereas their circulating monocytes were more potent for the production of IFNγ. [19]

In another randomized placebo-controlled human challenge study, we found that BCG vaccination induced genome-wide epigenetic reprograming of monocytes and protected against experimental infection with an attenuated yellow fever virus vaccine strain. Epigenetic reprogramming was accompanied by functional changes indicative of trained immunity. [14]
In clinical studies followed by clinical endpoints, adolescents vaccinated with BCG have shown a 70% decrease in the incidence of respiratory tract infections compared to placebo.[9] Consecutive BCG vaccination for 3 months in elderly individuals reduced the incidence of acute upper tract respiratory infections by 80% (95%CI=22-95%).[10] BCG vaccine in immunocompetent adult people is considered safe, even in latently infected adults with prior infant BCG vaccination. [15,16] In a randomized controlled trial that compared revaccination with BCG versus placebo, no serious adverse events were observed in the BCG arm. [9]

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

No

d. Selectivity of the mechanism to target tissue in animals and/or human beings

The effect of BCG is restricted to immune cells, with no effects exerted in other tissues.

e. Analysis of potential effect

The effect of BCG on the susceptibility to / or severity of infection with SARS-CoV-2 is unknown. Previous clinical studies with BCG vaccination that have shown a reduction of respiratory tract infection between 30 to 70%. We hypothesize that BCG could alter the clinical course of SARS-CoV-2 infection and demonstrate 60% efficacy in preventing infection with SARS-CoV2 in HCWs. As mentioned previously, based on a previous trial, we expect rare serious adverse events.

f. Pharmacokinetic considerations

BCG is injected intradermally in the skin at the superior region of the arm, and it is known to persist at the site of injection for up to 4 weeks.

g. Study population

Health-care workers face an elevated risk of exposure to- and infection of- SARS-CoV-2.3. Of 75,465 laboratory-confirmed cases, 2,055 (2.7%) were reported among health care workers from 476 hospitals across China. The majority of cases (77.8%) were found in the working age (30–69 years).[1]

h. Interaction with other products

No known interactions.

i. Predictability of effect

Multiple studies, among which randomized trials showed favorable *in vitro* and *in vivo* protective effects of BCG vaccination in the response to infections, among which viral infections. The objective of the trial is to evaluate if the same effect is observed when using BCG to improve the clinical course of SARS-CoV-2 infection. The safety profile of BCG vaccines has been studied extensively and no severe hazardous effects are expected. [15]

j. Can effects be managed?

The beneficial effects of BCG will be straight forward to register. The local side-effects are minimal and easy to manage. Management of rare and serious adverse events (suppurative lymphadenitis, disseminated BCG and anaphylaxis) will occur by the study participant's primary medical provider in conjunction with expert advice from infectious disease physicians part of this study.

12. REGULATORY REQUIREMENTS/REPORTING, MONITORING AND PUBLICATION

a. Financial Disclosure

No financial disclosures to be made. No other commercial support is expended to conduct this study. Merck manufactures the investigational product used in this study and it (or the placebo) will provided for free to subjects participating in this investigation.

b. IRB Approval

Prior to initiating the study, the investigators will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the investigator for IRB approval prior to implementation. Annual progress reports will be submitted to the IRB annually.

c. Ethical conduct of the study

The Investigator agrees, to adhere to the instructions and procedures described in the protocol and conduct the study in accordance with the Code of Federal Regulations (21 CFR Parts 11, 50, 54, 56, 312, 314, and 320), which originate from the ethical principles laid down in the current revision of the Declaration of Helsinki, GCP, and policies and procedures as outlined by the ethical requirements for IRB review and informed consent forms.

d. Ethics and regulatory review

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. The investigator will notify the IRB of deviations from the protocol or serious adverse events/unanticipated problems occurring in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval /renewal throughout the duration of the study. The IRB will be notified of completion or termination of this study and sent a copy of the study synopsis in accordance with applicable timelines.

e. Informed consent

The investigator, sub-investigators, and/or designated staff will explain all aspects of the study in lay language and answer all of the subject's questions regarding the study. If the subject desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. All study subjects will be given a copy of the signed Informed Consent(s). Prior to performing any study-related activities under this protocol, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. The background of the proposed study, procedures, benefits and risks and voluntariness of this study will be explained to the subject. The investigator, sub-investigators, and designated staff will explain all aspects of the study in lay language and answer all of the subject's questions regarding the study. Full confidentiality of subjects and subject records will be provided according to institutional guidelines. All study subjects will be given a copy of the Informed Consent(s) and given sufficient time to consider whether to participate in the study. The signed consent form will be retained with the study records.

As this study recruits employees, the ICF will also clearly state that involvement is voluntary and not include any coercive language. It will clearly be stated that there will be no favoritism, consternation, retribution or compelling socioeconomic benefits with the participation or refusal to participate in this study (PMID: 23533983).

f. Incentives and Research Related Injury

Patients will not be compensated for participating in this study. Participants will not be charged for the cost of the vaccination (or placebo). If a subject are injured, necessary facilities, emergency treatment and professional services will be available to them, just as they are to the general community.

In the event of injury resulting from this research, or negligence of local study personnel, the study team nor their institution are able to offer financial compensation nor to absorb the costs of medical treatment.

Procedures and treatment for clinical care related to potential adverse events will be billed to the subject and/or their insurance or applicable third party.

g. Changes to the Protocol and/or Informed Consent

Changes to the research covered by this protocol must be implemented by formal protocol amendment. Protocol amendments must not be implemented without prior IRB approval. When the change(s) involve only logistic or administrative aspects of the study, the IRB only needs to be notified. The data recorded on the CRF and source documents will reflect any departure from the protocol and the source documents will describe the departure and the circumstances requiring it.

A 'substantial amendment' is defined as an amendment to the terms of the IRB application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

h. Annual progress report

The sponsor-investigator will submit a summary of the progress of the trial to their IRB once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

i. Training of site study personnel

The Investigator will assure research activities, including those study-related duties delegated and will be performed by appropriately qualified individuals. The Investigator will assure that study staff will demonstrate due diligence in recruiting and screening study subjects.

The investigator will maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Delegation of Authority Form. The investigator and study staff will be responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by applicable regulatory authorities, including completed case report forms, subject identification list, study files and all correspondence to and from the IRBs.

j. Study Management

Each site Investigator will assure proper implementation and conduct of the study will be performed according to the currently approved study protocol.

k. Data Management, Handling, Storage and Security of data and documents

Data will be handled confidentially. A subject identification code list based will be used to link the data to the subject. The key to the code will be safeguarded by each site in a designated location. The electronic CRF (eCRF) are completed on an ongoing basis during the study. The eCRF will be managed via a secure and confidential system (RedCap).

The site principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The site principal investigator is also responsible for maintaining any source documentation related t

The investigator is responsible for complying with the requirements for all assessments and data collection as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required data collection and are unable or unwilling to complete, the investigator or study staff can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

The investigator and master file and the electronic data from the eCRF will be stored for a duration of 7 years. All information, data, and results that originate from this study may not be disclosed without the written permission of the principal investigator.

l. Temporary halt and end of study report

The sponsor will notify the BCM IRB immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the BCM IRB within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the the BCM IRB. The sponsor will notify the BCM IRB of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last registration in the mobile application. The sponsor will notify the BCM IRB immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the BCM IRB and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the BCM IRB.

m. Monitoring and Quality Assurance

We classify this trial as a low risk study, with a negligible risk because the vaccine is already FDA-approved, and has been shown to be safe in over 3 billion previously administered doses. It has a good safety profile.

n. Audits and Inspections

The Investigator will assure that study staff cooperate with monitoring and audits. The Investigator agrees to allow auditing of all essential clinical study documents by the FDA or other appropriate regulatory authorities. Auditing visits will be scheduled with the appropriate staff at mutually agreeable times as applicable.

o. Confidentiality and Reporting of Results

To maintain subject confidentiality, all data submitted for the current study will be coded using numeric identifiers only. Only on-site research staff will have access to records that may

identify subjects. Any paper research and clinical records will be stored on site in a locked cabinet in a secure location. Electronic records will be accessible only by data management staff, clinical monitors and active site personnel who have furnished the required training and credentials. Subject information will not be released without written permission, except as necessary for monitoring by the FDA.

By participating in this protocol, the Investigator agrees that within local regulatory restrictions and ethical considerations or any regulatory agency may consult and/or copy study documents in order to verify data.

p. Public disclosure and publication policy

The results of this study will be disclosed unreservedly at the end of the study. Results that are important for public health will be notified to the competent authorities as soon as possible (RIVM, WMO). The trial will be registered in a public trial registry before the first patient is consented. A description of this clinical trial will be available on http ://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify subjects. At most, the Web site will include a summary of the results. Prospective and current subjects can search this Web site at any time.

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Exhibit B

MD Anderson Cancer Center

Statement of Work

Dr. Ashish Kamat will serve as the Primary PI and work with co-PIs and **research team** at MD Anderson Cancer Center to collaborate with TAMU on the "BCG as Defense Against SARS-COVID19 (BADAS)" Trial. Dr. Kamat is an international expert and leader in treating bladder cancer patients with intravesical BCG treatments and has extensively published on this. He has been intimately involved in the design of the study from the start and has played a critical role in providing guidance for appropriate resource allocation of BCG vaccine via patient advocacy since, in the US, BCG is used almost exclusively for bladder cancer, and there is an ongoing shortage.

Dr. Kamat and research team will be responsible for accruing approximately 150 participants to the study, follow them for signs and symptoms of COVID-19 infection, collection of blood samples for serologies at baseline and monthly throughout the study, and providing vaccinations according to randomized treatment assignments.

Dr. Jianjun (JJ) Gao, has extensive experience in immunologic assays and will serve as co PI and supervise the study of the comprehensive antibody profiles in the plasma of study subjects to determine: 1) antibody profiles associated with the susceptibility of patients to covid-19 infection; 2) antibodies corresponding to protection from covid-19 infection without and with BCG vaccination; 3) specific peptides from BCG and/or covid-19 that generate antibodies for protection against covid-19.
Dr. Kamat will be responsible for the safety of participants and compliance of the study at MD Anderson and along with the MD Anderson research team, will coordinate all study activities with Dr. Cirillo.

As consideration for the work described in this Exhibit, TAMHSC agrees to pay MD Anderson a fixed price amount in accordance with the following payment schedule:

50%	Due upon execution of this Agreement
25%	Due within 6 months of the Effective Date
25%	Due upon completion of the Study

Collaborator shall submit invoices via email to: com-businessaffairs@tamu.edu.

Exhibit C

Baylor College of Medicine

The Baylor College of Medicine and the Global TB Research Program will work with the BCG as Defense Against SARS-COVID19 (BADAS) study PIs to implement this study. We aim on recruiting at least 350 study participants from Houston. Participants will be followed for 6 months via daily symptom screen (via RedCap) and will have monthly dried blood spot collected to evaluate for asymptomatic sero-conversion. If participants develop symptoms, they will be referred for active disease testing. Participants will have the option of donating plasma and PBMCs at baseline, 3 and 6 months. Dr. DiNardo will be responsible for running, implementing, analyzing the flow cytometry based multidimensional immune profiling and DNA methyl EPIC arrays on ~15-30 participants who a) develop symptomatic disease, b) develop asymptomatic sero-conversion and c) remain asymptomatic and do not sero-convert. Dr. DiNardo and Coarfa will coordinate all study activities with Dr. Cirillo.

As consideration for the work described in this Exhibit, TAMHSC agrees to pay BCM a fixed price amount in accordance with the following payment schedule:

50%	Due upon execution of this Agreement
25%	Due within 6 months of the Effective Date
25%	Due upon completion of the Study

Collaborator shall submit invoices via email to: com-businessaffairs@tamu.edu.

Exhibit D

Cedars-Sinai Medical Center

SUMMARY

Rationale: Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is spreading rapidly throughout the world. A large epidemic will seriously challenge the available hospital capacity, and this will be augmented by infection of healthcare workers (HCW). Strategies to prevent infection and disease severity of HCW are, therefore, desperately needed to safeguard continuous patient care. Bacille Calmette-Guérin (BCG) is a vaccine against tuberculosis, with protective non-specific effects against other respiratory tract infections in in vitro and in vivo studies, and reported morbidity and mortality reductions as high as 70%. Furthermore, in our preliminary analysis, areas with existing BCG vaccination programs appear to have lower incidence and mortality from coronavirus disease (COVID-19).1 We hypothesize that BCG vaccination can reduce HCW infection and disease severity during the epidemic phase of SARS-CoV-2.

Objectives:

- Primary objective: To measure the efficacy of BCG vaccination among HCW in preventing infection with CARS-CoV-2.
- Secondary objective: To measure the efficacy of BCG vaccination among HCW in mitigating the severity of COVID-19.

Study design: A placebo-controlled adaptive multi-center randomized controlled trial.
Study population: High-risk HCW with direct patient contact, defined as physician assistants, respiratory therapists, nurses, physicians or other HCWs working at emergency rooms, ICUs and in locations within hospitals where SARS-CoV-2-infected patients are treated.
Intervention: Participants will be randomized between intradermal administration of BCG vaccine or placebo in a 1:1 ratio. Total 400 health care workers will be enrolled.

Study endpoints:

- Primary endpoint: incidence of SARS-CoV-2 infection following BCG vaccination compared to placebo.
- Secondary endpoint: COVID-19-related disease severity following BCG vaccination compared to placebo.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Based on previous experience and randomized controlled trials in adult and elderly individuals, the risks of BCG vaccination are considered low. The objective of this trial is to evaluate the beneficial effects of BCG vaccination in high-risk health care workers through a mitigated clinical course of COVID-19. The primary endpoint and the adaptive design with frequent interim analyses facilitate maximum efficiency of the trial, so that results can inform policy making during the ongoing epidemic.

As consideration for the work described in this Exhibit, TAMHSC agrees to pay CSMC a fixed price amount in accordance with the following payment schedule:

50% Due upon execution of this Agreement

25% Due within 6 months of the Effective Date
25% Due upon completion of the Study

Collaborator shall submit invoices via email to: com-businessaffairs@tamu.edu.

Exhibit E
Data Use Agreement

This Data Use Agreement ("DUA") is entered into by the parties to this Agreement for purposes of complying with the federal Standards for Privacy of Individually Identifiable Health Information set forth at 45 C.F.R. Parts 160 and 164 (the "Privacy Standards").

1. Each receiving party would like to use certain health information maintained by the providing party as described in the Protocol for the Study in the form of a Limited Data Set for purposes of performing the Study (the "Purpose").

2. Definitions. The following capitalized terms have the meaning ascribed to them herein and if not defined herein, the definition provided in the Privacy Standards:

2.1. "Breach" means the unauthorized acquisition, access, use, or disclosure of unsecured Protected Health Information ("PHI") in a manner not permitted under the Privacy Standards that poses more than a low probability that the PHI has been compromised. The party with the breach notification responsibility under HIPAA will determine when a breach occurs.

2.2. "HIPAA" means the Health Insurance Portability and Accountability Act of 1996.

2.3. "Individual" means the person who is the subject of the Protected Health Information

2.4. "Limited Data Set" or "LDS" is defined in 45 C.F.R. § 164.514(e).

2.5. "Privacy Standards" means the Standards for Privacy of Individually Identifiable Health Information set forth at 45 C.F.R. Parts 160 and 164.

2.6. "Protected Health Information or PHI" is defined in 45 C.F.R. § 160.103.

2.7. "Research" is defined in 45 C.F.R. § 164.501.

2.8. "Required by Law" means a mandate contained in law that compels a use or disclosure of PHI and that is enforceable in a court of law.

3. Receiving Party Obligations Regarding the Limited Data Set. Each receiving party agrees to comply with all applicable federal and state privacy and security laws and further agrees:

3.1. not to use or disclose the Limited Data Set except as necessary to fulfill the Purpose other than as permitted by this Agreement or otherwise Required by Law;

3.2. to use appropriate safeguards to prevent use or disclosure of the Limited Data Set other than as permitted by this Agreement;

3.3. to immediately report to the providing party any use or disclosure of the Limited Data Set not permitted by this Agreement of which the receiving party becomes aware, including any unauthorized acquisition of computerized data that compromises the security, confidentiality, or integrity of information in the Limited Data Set. If any unanticipated use or disclosure of the Limited Data Set occurs, the receiving party shall cooperate and assist the disclosing party in determining, in an expedited manner, the date, nature, content, and extent of such unanticipated use or disclosure. In the event the unanticipated use or disclosure of the Limited Data Set constitutes a Breach, the receiving party shall cooperate and assist the disclosing party with the breach reporting process in the manner reasonably requested by the disclosing party;

3.4. to ensure that any agents to whom it provides the Limited Data Set agree to the same restrictions and conditions that apply to the receiving party with respect to the Limited Data Set; and

3.5. not to identify any Individuals or contact such Individuals.

4. Return or Destruction of LDS. Given that it is not feasible to return or destroy the Limited Data Set, each receiving party agrees to maintain the confidentiality of the Limited Data Set as set forth in this Agreement and the HIPAA Privacy Standards for as long as such receiving party retains the Limited Data Set.

5. Termination for Breach. If the receiving party breaches any provision in this Agreement, the disclosing party may, at its option, access and audit the records of the receiving party related to its use and disclosure of the Limited Data Set, require the receiving party to submit to monitoring and reporting, and such other conditions as the providing party may determine is necessary to ensure compliance with this Agreement, or the providing party may terminate this Agreement as of any date.

Any notices for Breach for any Limited Data Set provided by MD Anderson shall be made via U.S. Mail or express courier or via facsimile as follows: The University of Texas M. D. Anderson Cancer Center, Institutional Compliance Office, Attn: Privacy Officer, Unit 1640, P.O. Box 301407, Houston, Texas 77230-1407, Fax No. 713-563-4324.

6. Liability. Except to the extent prohibited by law, the receiving party assumes all liability for damages which may arise from its use, storage or disposition of the Limited Data Set.

7. Survival. Paragraphs 3-8 of this DUA survive termination of this Agreement.

8. Miscellaneous. Each providing party retains all rights to the Limited Data Set that such providing party discloses to a receiving party. This Agreement may not be changed or modified in any manner except by an instrument in writing signed by a duly authorized representative of each of the parties. The parties, however, agree to amend this agreement from time to time as needed to assure compliance with the Privacy Standards.