START PAGE

MARIE SKŁODOWSKA-CURIE ACTIONS

Individual Fellowships (IF)
Call: H2020-MSCA-IF-2015

PART B

“ProDeepCAD”

This proposal is to be evaluated as:

Standard GF

TABLE OF CONTENTS

0 LIST OF PARTICIPANTS

Participants	Legal Entity Short Name	Academic	Non-academic	Country	Dept. / Division / Laboratory	Supervisor	Role of Partner Organisation
Beneficiary							
- NAME							
Partner Organisation							
- NAME							

Data for non-academic beneficiaries

Name	Location of research premises (city / country)	Type of R&D activities	No. of fulltime employees	No. of employees in R&D	Website	Annual turnover (approx. in Euro)	Enterprise status (Yes/No)	SME status (Yes/No)

Note that:

- Any inter-relationship between different participating institutions or individuals (e.g. family ties, shared premises or facilities, joint ownership, financial interest, overlapping staff or directors, etc.) must be declared and justified in this part of the proposal;
- The information in the table for non-academic beneficiaries must be based on current data, not projections;
- The data provided relating to the capacity of the participating institutions will be subject to verification during the Grant Agreement preparation phase.

1 SUMMARY

That will be the abstract of the proposal

2 EXCELLENCE

2.1 Quality, innovative aspects and credibility of the research

2.1.1 Introduction

In Europe, prostate cancer is reported to be the most frequently diagnosed cancer of men and thus one of the leading cause of death of cancer[1]. Currently, addressing this issue is a major public debate, in which the implementation of appropriate screening methods and subsequent treatments is key.

In this regard, the European Randomised Study of Screening for Prostate Cancer (ERSPC) is conducted to investigate the potential benefits of a population-based screening[2]. The screening consists of a Prostate-Specific Antigen (PSA) test and depending of the PSA level measured, an additional "blind" biopsy is carried out. Despite the fact of a significant reduction of the prostate cancer mortality, the screening strategy employed suffers of a high rate of over-diagnosis and over-treatment[3], due to the fact that prostate cancer growth is characterized by two main types of evolution: slow and fast. The slow-growing tumours account for up to 85 % of all cancers and stay confined to the prostate gland, while the fast-growing tumours rapidly develop and metastasise to other organs, significantly affecting the morbidity and mortality rate. Furthermore, prostate cancer is more likely to develop in specific regions of the prostate: around 70-80 % of prostate cancers originate in the Peripheral Zone, whereas 10-20 % in the Central Gland (CG), but appear to be more aggressive and more likely to invade other organs. **Thus, additionally to cancer detection, the screening methods need to provide an estimate of the cancer aggressiveness to allow clinicians to act accordingly.**

In addition, the investigators of the ERSPC have come to the conclusion that the use of *"multi-parametric Magnetic Resonance Imaging (MRI) and the development of new markers are the hope for the future"*. That is why, Computer-Aided Diagnosis (CAD) systems revolved around mono- and multi-parametric MRI are currently developed by the medical imaging community, and were recently reviewed by Lemaître *et al.*[4]. The CAD systems developed are designed under the same architecture as depicted in Fig. 1. The available MRI modalities during prostate exam are T_2-Weighted (T_2-W)-MRI, Diffusion Weighted (DW)-MRI, Dynamic Contrast-Enhanced (DCE)-MRI, and Magnetic Resonance Spectroscopy Imaging (MRSI). Additionally, Apparent Diffusion Coefficient (ADC) map is based on the computation of a coefficient derived from multiple DW-MRI. **Currently, no CAD system has been developed using all the available modalities and thus discarding their potential discriminating power to diagnose prostate cancer.**

The closest attempts used three of these modalities (i.e., T_2-W-MRI, DW-MRI, DCE-MRI) and discarded MRSI[5,6]. This latter, however, has been shown to be extremely helpful to grade cancer aggressiveness particularly in the CG[7], which is the most challenging zone in terms of cancer detection. **Furthermore, the current researches solely focus on the delineation of prostate cancers rather than on the cancer aggressiveness assessment.**

Therefore, the aim of this project is to design a CAD system able to both detect and assess prostate cancers using all currently available multi-parametric MRI modalities. drastically improve here The architecture of our CAD system will imply the following investigations:

1. Pre-processing to enhance the quality of MRI images (bias field correction, denoising, and normalisation),
2. Segmentation of prostate zones using multi-parametric MRI and deep-learning,

[1] J. Ferlay et al. "Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012". In: *European Journal of Cancer* 49.6 (2013), pp. 1374 –1403.

[2] F. H. Schroder et al. "Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up". In: *The Lancet* 384.9959 (2015), pp. 2027 –2035.

[3] C. Delpierre et al. "Life expectancy estimates as a key factor in over-treatment: the case of prostate cancer". In: *Cancer Epidemiol* 37.4 (2013), pp. 462–468; Schroder et al., "Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up".

[4] G. Lemaître et al. "Computer-Aided Detection and Diagnosis for Prostate Cancer based on mono and multi-parametric MRI: A review". In: *Computers in Biology and Medicine* 60 (2015), pp. 8 –31.

[5] G. Litjens et al. "Computer-iided detection of prostate cancer in MRI". in: *Medical Imaging, IEEE Transactions on* 33.5 (2014), pp. 1083–1092. ISSN: 0278-0062.

[6] S. Viswanath et al. "Enhanced multi-protocol analysis via intelligent supervised embedding (EMPrAvISE): detecting prostate cancer on multi-parametric MRI". in: *Proc. SPIE 7963, Medical Imaging 2011: Computer-Aided Diagnosis.* 2011.

[7] E. K. Vos et al. "Multiparametric Magnetic Resonance Imaging for Discriminating Low-Grade From High-Grade Prostate Cancer." In: *Investigative Radiology* (2015).

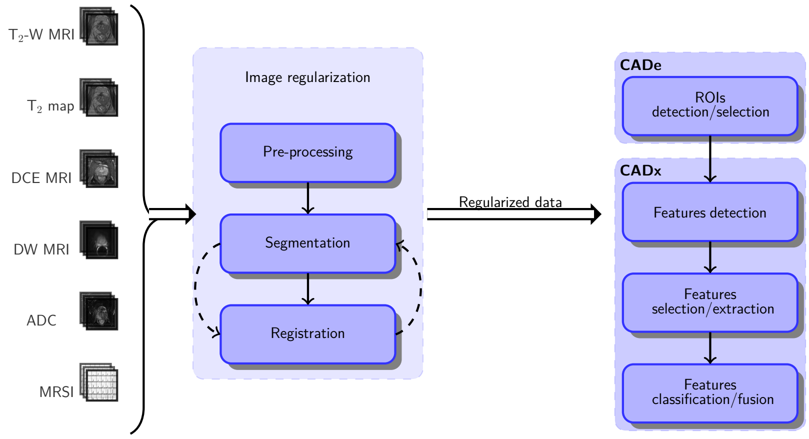

Figure 1: Common CAD framework based on MRI images used to detect prostate cancer.

3. Registration of multi-parametric MRI using spline-based non-linear differmorphism,
4. Detection and assessment of prostate cancers using using multi-parametric MRI and deep-learning,
5. Identification of markers by inspection of the neural-network and transfer to classical machine learning approach.
6. Grading using standard PI-RADS

These methodologies will be extensively presented and argued in Sect. 2.1.2.

2.1.2 Research methodologies

Data acquisition

Pre-processing MRI images are corrupted by different phenomena: (i) bias field, (ii) noise, and (iii) inter-patient variations. In this regard, particular attention to correct each of these drawbacks will be addressed.

MRI images are affected by the inhomogeneity of the MRI field called bias field, resulting in a smooth variation of the intensities. Although bias correction methods are commonly used to enhance brain MRI images[8], only one CAD system for prostate has reported to use such pre-processing[9]. The same authors performed an empirical evaluation of the state-of-the-art methods[10] concluding that N3 algorithm[11] yields to better classification results than other methods[12,13]. Recently, Lin *et al.*[14] proposed a method combining the N3 algorithm with the FCM algorithm[15] which outperforms the original methods in terms of breast segmentation. **Therefore, we will perform an empirical comparison of these state-of-the-art methods[16,17,18,19], by ensuring the benefits of the method of Lin *et al.* for our specific application.**

[8] U. Vovk, F. Pernus, and B. Likar. "A review of methods for correction of intensity inhomogeneity in MRI". in: *Medical Imaging, IEEE Transactions on* 26.3 (2007), pp. 405–421. ISSN: 0278-0062.

[9] S. Viswanath et al. "Integrating structural and functional imaging for computer assisted detection of prostate cancer on multi-protocol in vivo 3 Tesla MRI". in: *Society of Photo-Optical Instrumentation Engineers (SPIE) Conference Series*. Vol. 7260. Society of Photo-Optical Instrumentation Engineers (SPIE) Conference Series. Feb. 2009.

[10] S. Viswanath et al. "Empirical evaluation of bias field correction algorithms for computer-aided detection of prostate cancer on T2w MRI". in: *SPIE Medical Imaging*. International Society for Optics and Photonics. 2011, pp. 79630V–79630V.

[11] J. G. Sled, A. P. Zijdenbos, and A. C. Evans. "A nonparametric method for automatic correction of intensity nonuniformity in MRI data". In: *IEEE Trans Med Imaging* 17.1 (1998), pp. 87–97.

[12] M. Styner et al. "Parametric estimate of intensity inhomogeneities applied to MRI". in: *Medical Imaging, IEEE Transactions on* 19.3 (2000), pp. 153–165. ISSN: 0278-0062.

[13] M. S Cohen, R. M DuBois, and M. M Zeineh. "Rapid and effective correction of RF inhomogeneity for high field magnetic resonance imaging". In: *Human brain mapping* 10.4 (2000), pp. 204–211.

[14] M. Lin et al. "A new bias field correction method combining N3 and FCM for improved segmentation of breast density on MRIa)". In: *Medical physics* 38.1 (2011), pp. 5–14.

[15] M. N. Ahmed et al. "A modified fuzzy c-means algorithm for bias field estimation and segmentation of MRI data". In: *Medical Imaging, IEEE Transactions on* 21.3 (2002), pp. 193–199.

[16] Sled, Zijdenbos, and Evans, "A nonparametric method for automatic correction of intensity nonuniformity in MRI data".

[17] Styner et al., "Parametric estimate of intensity inhomogeneities applied to MRI".

[18] Cohen, DuBois, and Zeineh, "Rapid and effective correction of RF inhomogeneity for high field magnetic resonance imaging".

[19] Lin et al., "A new bias field correction method combining N3 and FCM for improved segmentation of breast density on MRIa)".

Apart of the bias field, MRI images are also degraded due to a Rician noise. Similarly to bias correction, only two CAD systems for prostate denoised images using wavelet-based techniques[20,21], offering a proper theoretical baseline for Rician corruption[22]. Non-Local Means-based denoising techniques have never been used for MRI prostate images, but extensively and successfully for other MRI applications[23]. **Thus, we will perform an empirical evaluation of the Non-Local Means-based techniques[24,25] and wavelet-based technique[26] to select the appropriate method to our application.**

CAD systems are based on machine learning classifiers which are trained to differentiate cancerous from healthy tissue. The classification performance of these classifiers highly relies on the consistency of the dataset. Subsequently, one can emphasize the desire to reduce the inter-patient variability of the MRI dataset. In this regard, each patient dataset needs to be standardised/normalised to common basis, modality by modality. Only two methods have been used in CAD for prostate: the first method consists in normalising the images via the z-score, while the second technique is based on a linear normalisation by parts[27]. Lemaître *et al.* [28] developed a normalisation technique using the Rician properties of the MRI signal, which outperforms the previous methods for T_2-W-MRI images. **Thus, we will extend this work to the other modalities DCE-MRI and DW-MRI**.

MRSI is a modality related to one dimensional signal, thus enhancing techniques differs from the one used in MRI. The MRSI spectra have to be corrected for several phenomena: phase correction, water and lipid residuals filtering, baseline correction, frequency alignment, and normalisation. This set of enhancement techniques already have been investigated by Lemaître *et al.*[29], in a study focusing solely on the MRSI modality for prostate cancer detection; **this knowledge will be the basis of MRSI enhancement.**

Segmentation To achieve robust cancer detection, the classification has to be carried out only on the prostate area, motivating the need to perform a segmentation of the organ in the MRI images. Furthermore, as mentioned in Sect. 2.1.1), the membership *a priori* of a voxel to a specific prostate zone has a high potential to increase the performance to evaluate the aggressiveness of prostate cancer. Therefore, the prostate zones need to be segmented instead of solely the prostate organ. In this regard, only the work of Litjens *et al.* performed a zonal segmentation of the prostate using probabilistic multi-atlas approach[30]. However, the segmentation was performed only considering the T_2-W-MRI modality and the ADC map. Moreover, although atlas-based methods are robust to intensity variations, they lack of accuracy in the boundary delineations[31]. The potential of machine learning methods to carry out such task is currently underestimated, but has been shown to be suitable in combination with the other approach[32]. **Thus, we will design a hybrid system based on Convolutional Neural Networks (CNN) and Active Shape Models using all multi-parametric images to perform zonal segmentation.** The choice of CNN is motivated by the recent breakthrough of deep-learning in multiple fields of computer vision. Deep-learning, however, has still not be extensively used in the field of medical imaging as attested by the organisation of the first workshop specifically dedicated to this topic at MICCAI 2015. Deep-learning relies on a data-driven training stage in which large amount of data are required, which is a serious drawback in medical imaging. However, this is the problematic tackled by the field of transfer learning which will allow to deploy deep-learning to medical imaging.

[20] S. Mallat. *A wavelet tour of signal processing, Third Edition: The sparse way*. 3rd. Academic Press, 2008. ISBN: 0123743702, 9780123743701.

[21] A. Pizurica et al. "A versatile wavelet domain noise filtration technique for medical imaging". In: *IEEE Trans Med Imaging* 22.3 (2003), pp. 323–331.

[22] R.D. Nowak. "Wavelet-based Rician noise removal for magnetic resonance imaging". In: *Image Processing, IEEE Transactions on* 8.10 (1999), pp. 1408–1419. ISSN: 1057-7149.

[23] J. V. Manjon et al. "MRI denoising using non-local means". In: *Med Image Anal* 12.4 (2008), pp. 514–523.

[24] J. V. Manjón et al. "New methods for MRI denoising based on sparseness and self-similarity." In: *Medical Image Analysis* 16.1 (Jan. 2012), pp. 18–27.

[25] P. Coupé et al. "Adaptive Multiresolution Non-Local Means Filter for 3D MR Image Denoising". In: *IET Image Processing* (Nov. 2011), accepted.

[26] Pizurica et al., "A versatile wavelet domain noise filtration technique for medical imaging".

[27] A. Madabhushi and J. K. Udupa. "New methods of MR image intensity standardization via generalized scale". In: *Med Phys* 33.9 (2006), pp. 3426–3434.

[28] This work is submitted for publication.

[29] G. Lemaître. "Absolute quantification at 3 T". MA thesis. Université de Bourgogne, Heriot-Watt University, Universitat de Girona, 2011.

[30] Litjens et al., "Computer-iided detection of prostate cancer in MRI".

[31] S. Ghose et al. "A survey of prostate segmentation methodologies in ultrasound, magnetic resonance and computed tomography images". In: *Comput Methods Programs Biomed* 108.1 (2012), pp. 262–287.

[32] S. Ghose et al. "Graph cut energy minimization in a probabilistic learning framework for 3D prostate segmentation in MRI". in: *Pattern Recognition (ICPR), 2012 21st International Conference on*. IEEE. 2012, pp. 125–128.

Registration In multi-parametric MRI, the data are collected in a sequential manner, involving a possible misalignment between the different modalities. Mitra *et al.*[33] developed an automatic multi-modal non-rigid registration method, which has been shown to outperform the state-of-the-art methods. This method was initially used for registration between T_2-W-MRI and Ultra-Sound prostate images, **therefore, we will extend this method to align our multi-parametric MRI dataset.**

Detection and assessment Up to know, the CAD systems developed solely focus on the detection of prostate cancers, omitting a real-assessment of the potential lesions detected. The detection of cancers is commonly performed using machine leaning classifiers, designing frameworks as depicted in Fig. 1. These frameworks rely on two compulsory stages and an intermediate optional one: (i) features detection, (ii) features selection/extraction and (iii) features classification. Lemaître *et al.* extensively reviewed researches carried out in each of this stage for the development of CAD for prostate cancer[34]. These stages are organised in a sequential manner and thus stages upstream part of the features classification will have a tremendous importance on the classification performance. Consequently, the use of discriminative features is certainly key and most probably the bottleneck of CAD systems, justifying the attention given by researchers to evaluate multitude of low- and high-level visual features, inspired by computer vision or biology. As aforementioned, deep-learning has been recently shown to one of the most successful machine learning technique for broad types of classification tasks. CNN has the ability to generate automatically low- and high-level visual features in the network itself[35] by only supplying the raw data as inputs. Furthermore, CNN can be trained using the Gleason grade obtained through biopsy in order to get an assessment of the aggressiveness of the cancer. **Thus, we will use CNN to perform the detection and the assessment of prostate cancer. In addition, we will investigate the low- and high-level features to potentially find new bio-markers which can be used by clinicians or other machine learning methods.**

Evaluation using PI-RADS The European Society of Urogenital Radiology together with the American College of Radiology recently published the Prostate Imaging and Reporting and Data System (PI-RADS), which is a standard way to assess and report prostate lesions using multi-parametric MRI. This standard allows to report a score depending of multiple criteria such as signal intensity, texture, size of lesion, modality, prostate zones, etc. None of the current CAD systems offer a PI-RADS score when detecting potential lesions in multi-parametric MRI. **Thus, we will report the output of our classification framework in terms of PI-RADS score, applying the provided criterion.**

2.2 Clarity and quality of transfer of knowledge/training for the development of the researcher in light of the research objectives

2.3 Quality of the supervision and the hosting arrangements

Qualifications and experience of the supervisor(s)

Career development

2.4 Capacity of the researcher to reach and re-enforce a position of professional maturity in research

3 IMPACT

3.1 Enhancing research- and innovation-related human resources, skills, and working conditions to realise the potential of individuals and to provide new career perspectives

In this section, please explain the impact of the research and training on the Experienced Researcher's career. The fellowship, including any secondments in Europe should maximise the impact on the researcher's activity on European society, including the science base and/or the economy, in a manner appropriate to the research field.

3.2 Effectiveness of the proposed measures for communication and results dissemination

Required sub-headings:

[33] J. Mitra et al. "A spline-based non-linear diffeomorphism for multimodal prostate registration". In: *Med Image Anal* 16.6 (2012), pp. 1259–1279.

[34] Lemaître et al., "Computer-Aided Detection and Diagnosis for Prostate Cancer based on mono and multi-parametric MRI: A review".

[35] Matthew D. Zeiler and Rob Fergus. "Visualizing and Understanding Convolutional Networks". In: *CoRR* abs/1311.2901 (2013).

Communication and public engagement strategy of the action
Dissemination of the research results
Exploitation of results and intellectual property

Concrete plans for the above must be included in the Gantt Chart. The new knowledge generated by the action should be used wherever possible to enhance the career of the researcher, to advance research, to foster innovation, and to promote the research profession to the public. The following sections of the European Charter for Researchers refer specifically to public engagement and dissemination:

Public engagement Researchers should ensure that their research activities are made known to society at large in such a way that they can be understood by non-specialists, thereby improving the public's understanding of science. Direct engagement with the public will help researchers to better understand public interest in priorities for science and technology and also the public's concerns.

Dissemination, exploitation of results All researchers should ensure, in compliance with their contractual arrangements, that the results of their research are disseminated and exploited, e.g. communicated, transferred into other research settings or, if appropriate, commercialised. Senior researchers, in particular, are expected to take a lead in ensuring that research is fruitful and that results are either exploited commercially or made accessible to the public (or both) whenever the opportunity arises.

4 IMPLEMENTATION

4.1 Overall coherence and effectiveness of the work plan

The proposal should be designed in the optimal way to achieve the desired impact. A Gantt Chart should be included in the text where the following should be listed:

- Work Packages description;
- List of major deliverables;
- List of major milestones;
- Secondments if applicable.

The schedule should be in terms of number of months elapsed from the start of the project.

4.2 Appropriateness of the management structure and procedures, including quality management and risk management

Develop your proposal according to the following lines:

- Project organisation and management structure, including the financial management strategy, as well as the progress monitoring mechanisms put in place;
- Risks that might endanger reaching project objectives and the contingency plans to be put in place should risk occur.

The following could be also included in the Gantt Chart:

- Progress monitoring;
- Risk management;
- Intellectual Property Rights (IPR).

4.3 Appropriateness of the institutional environment (infrastructure)

Give a description of the legal entity/ies and its main tasks (per participant). Explain why the fellowship has the maximum chance of a successful outcome.

NB: Each participant is described in Section 6. This specific information should not be repeated here.

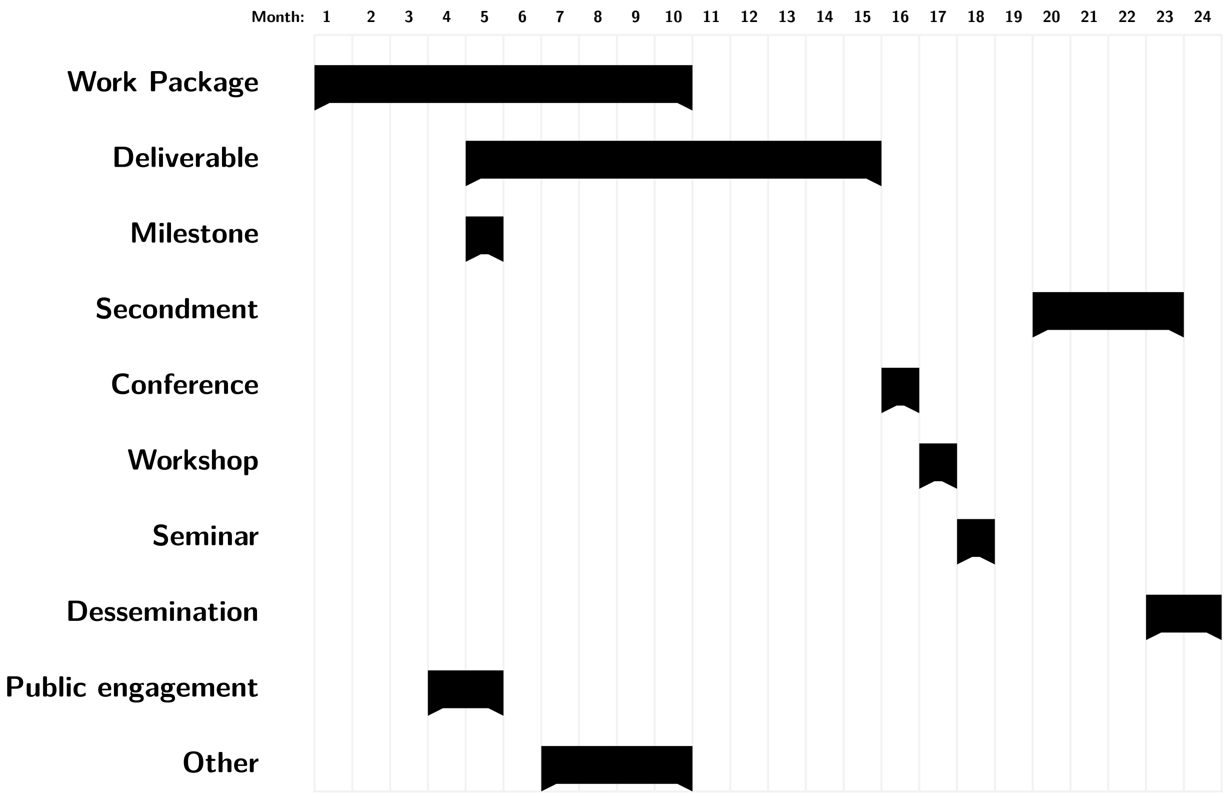

Figure 2: Example Gantt Chart

4.4 Competences, experience and complementarity of the participating organisations and institutional commitment

Here describe how the fellowship will be beneficial for both the Experienced Researcher and host organisation(s).

- Commitment of beneficiary and partner organisations to the programme (for partner organisations, please see also section 6)

Partner organisations: The role of Partner organisations in MS/AC for secondments and their active contribution to the research and training activities should be described.

5 CV OF THE EXPERIENCED RESEARCHER

This section should be limited to maximum 5 pages and should include the standard academic and research record. Any research career gaps and/or unconventional paths should be clearly explained so that this can be fairly assessed by the independent evaluators. The Experienced Researchers must provide a list of achievements reflecting their track, and this may include, if applicable:

1. Publications in major international peer-reviewed multi-disciplinary scientific journals and/or in the leading international peer-reviewed journals, peer-reviewed conference proceedings and/or monographs of their respective research fields, indicating also the number of citations (excluding self-citations) they have attracted.
2. Granted patent(s).
3. Research monographs, chapters in collective volumes and any translations thereof.
4. Invited presentations to peer-reviewed, internationally established conferences and/or international advanced schools.
5. Research expeditions that the Experienced Researcher has led.
6. Organisation of International conferences in the field of the applicant (membership in the steering and/or programme committee).
7. Examples of leadership in industrial innovation.
8. Prizes and Awards.

6 CAPACITIES OF THE PARTICIPATING ORGANISATIONS

All organisations (whether beneficiary or partner organisation) must complete the appropriate table below. Complete one table of maximum one page for the beneficiary and half a page per partner organisation (min font size: 9). The experts will be instructed to disregard content above this limit.

Beneficiary X	
General Description	
Role and Commitment of key persons (supervisor)	(Including names, title, qualifications of the supervisor)
Key Research Facilities, Infrastructure and Equipment	(Demonstrate that the team has sufficient facilities and infrastructure to host and/or offer a suitable environment for training and transfer of knowledge to recruited Experienced Researcher)
Independent research premises?	
Previous Involvement in Research and Training Programmes	
Current involvement in Research and Training Programmes	(Detail the EU and/or national research and training actions in which the partner is currently participating)
Relevant Publications and/or research/innovation products	(Max 5)

Partner Organisation Y	
General Description	
Key Persons and Expertise (supervisor)	
Key Research facilities, infrastructure and equipment	
Previous and Current Involvement in Research and Training Programmes	
Relevant Publications and/or research/innovation product	(Max 3)

ENDPAGE

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[Standard EF]