NARAYANA MEDICAL COLLEGE

A Webinar on

"Scientific Writing & Searching Medical Databases"

Conducted by Narayana Translational Research Centre (NTRC)

on 17th November, 2020 at 10 am to 11 am

PANELIST

Patron: **Dr. Surya Prakash Rao, Professor and Dean**

Speaker: **Dr. Ishima Badhwar, M.Tech, M.B.B.S, Clinical Consultant Elsevier, Head of Customer engagement division, Elsevier India and South Asia**

Panelists from Elsevier: **Mr. Durga Ranganath & Mrs. Sheena Warrier, Elsevier**

Convenor: **Dr. Sivakumar Vijayaraghavalu,** Professor and Head, NTRC; has briefed about the speaker to the participants as follows –

ABOUT THE SPEAKER

Dr. Ishima Badhwar holds the degree both in two major disciplines - Medicine and Engineering, a unique and rare profiles in India. She did her MBBS from Aligarh Muslim University, one of the oldest University in India established in 1875 and ranks 18th in the nation. Her quest for research led her to obtain a Master's degree in Bioengineering from Indian Institute of Technology, Kanpur, one of the most prestigious IITs in India and ranks 6th in the nation. Getting admissions in such an organization is highly competitive, she cracked it and this shows her competency. Thereafter she has worked in multiple organizations across medical devices, pharmaceuticals and now in publishing. She is a clinical consultant with Elsevier and is currently heading the Customer Engagement Division for Elsevier India and South Asia. She has a

decade of experience in healthcare. She is passionate about medical writing and providing solutions for supporting the researchers. She has conducted multiple sessions on Scientific Writing and various Elsevier research solutions. Hence we feel she will be appropriate speaker for our Medical Institution and we welcome Dr. Ishima to deliver the talk post inaugural speech by our respected Dean Dr. S.P. Rao and requested him to take over the session. He welcomed the Elsevier team and thanked them for offering to give a talk and briefed about the scientific writing.

After his talk, Dr. Ishima took over the session and she briefed on the framework of scientific writing, how to write research reports and articles and various methods to be adopted while writing articles to journals. Then she asked the participants - why is it important to publish science? After a short pause she answered it as – *"Because research*

and diffusion of knowledge are the fuel to the country's progress". She concisely told about the peer review- and editorial- process. She discussed on why the editors reject the article? She explained the publishing tips given by Peter Thrower PhD (Editor – in Chief of the Journal – Carbon) and eight reasons why the journal editors rejected your article? She also explained, how and when to write the different components of the manuscript such as - Title, Abstract, Introduction, Methods, Results, Discussion and Conclusions, References and Supplementary documents. She also focused on the inclusion of various important aspects in every component of the scientific articles, especially methodology, results and discussion parts. She informed participants that the instructions to authors may vary from journal to journal, hence to read it carefully prior submitting the manuscript to the journal of interest, if it got rejected and the same article submitting to another journal then modify as per the authors instruction of that

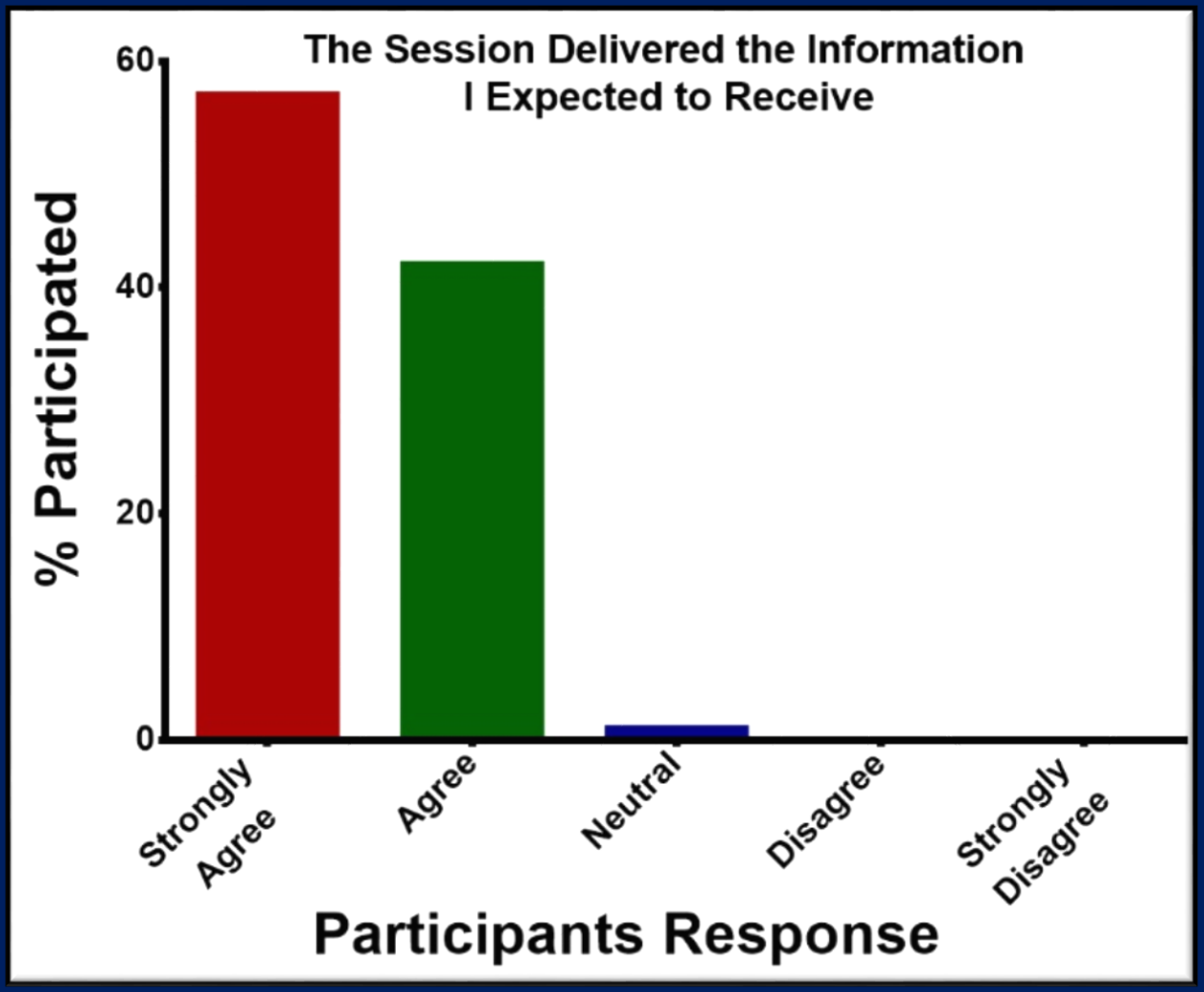
journal. Further, she stated that most of the researcher do mistakes in formatting the references, hence care should be taken to avoid such mistakes and it is wise to use any of the existing online/offline reference managers – such as Cite This for Me, Mendeley, bibme, Zotero and EndNote basic. She touch-based on the plagiarism software to avoid plagiarism and advised to rephrase the sentences taken from the reference articles. She showed some of the well-constructed research articles as an example to the audience. Finally, the webinar ended with a vote of thanks by the Convenor.

Registrants Profile –

Total two hundred and forty-four registrants were from India (95%) and other countries (5%) which includes - Bahrain, Sweden, Japan and Malaysia. Indian registrants were from across the country with higher percentage from Andhra Pradesh (75%), followed by Tamil Nadu (11%), and Telangana (9%); rest of the 2% are from the following states – Maharashtra, Karnataka, New Delhi and Haryana.

Participants poll about the webinar and the power point of the presentation of the speaker is given below.

Participants Poll Results


The Session Delivered the Information
I Expected to Receive
% Participated
60
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Strongly Agree
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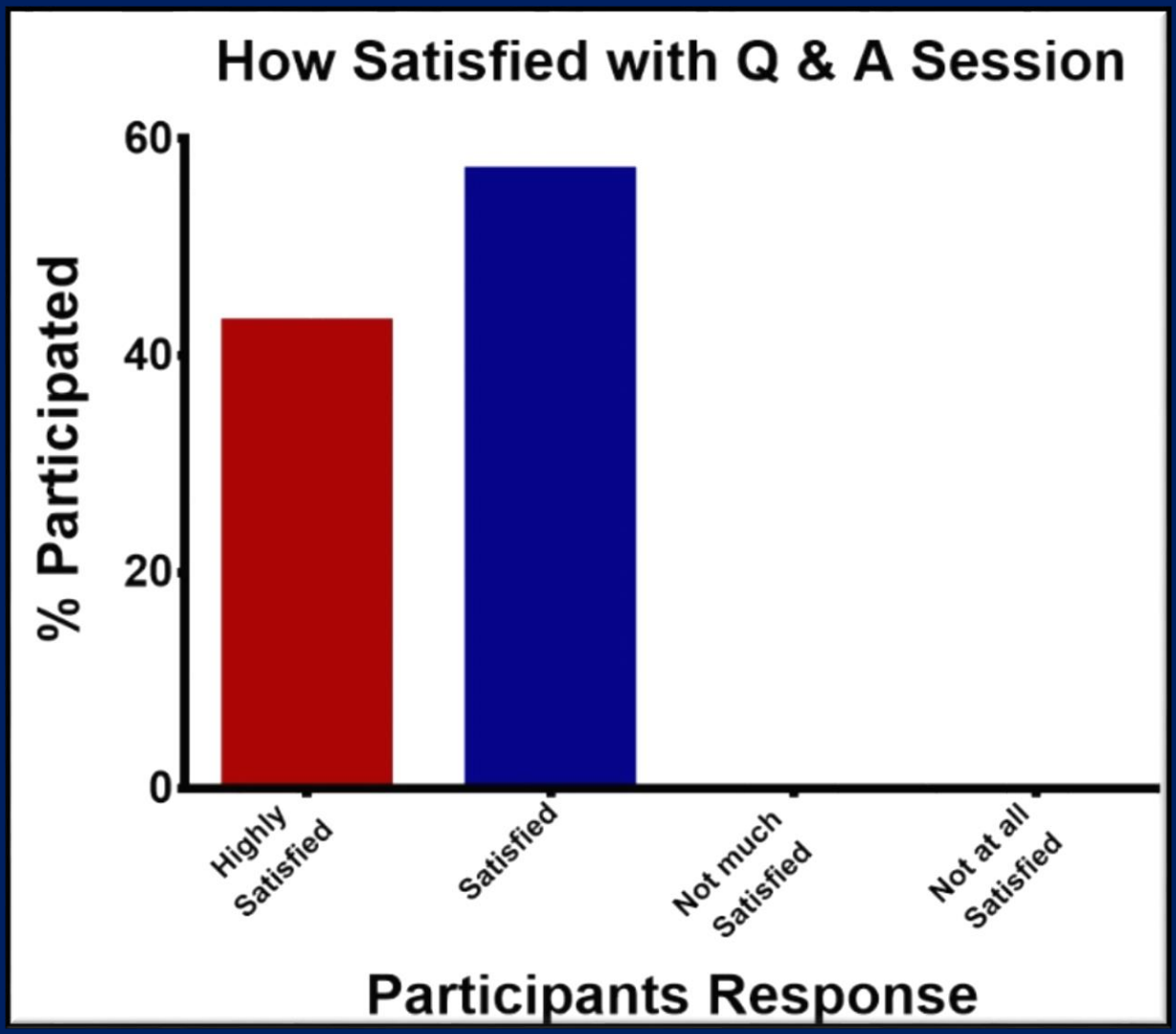
Participants Response


How Satisfied with Q & A Session
% Participated
60
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Highly Satisfied
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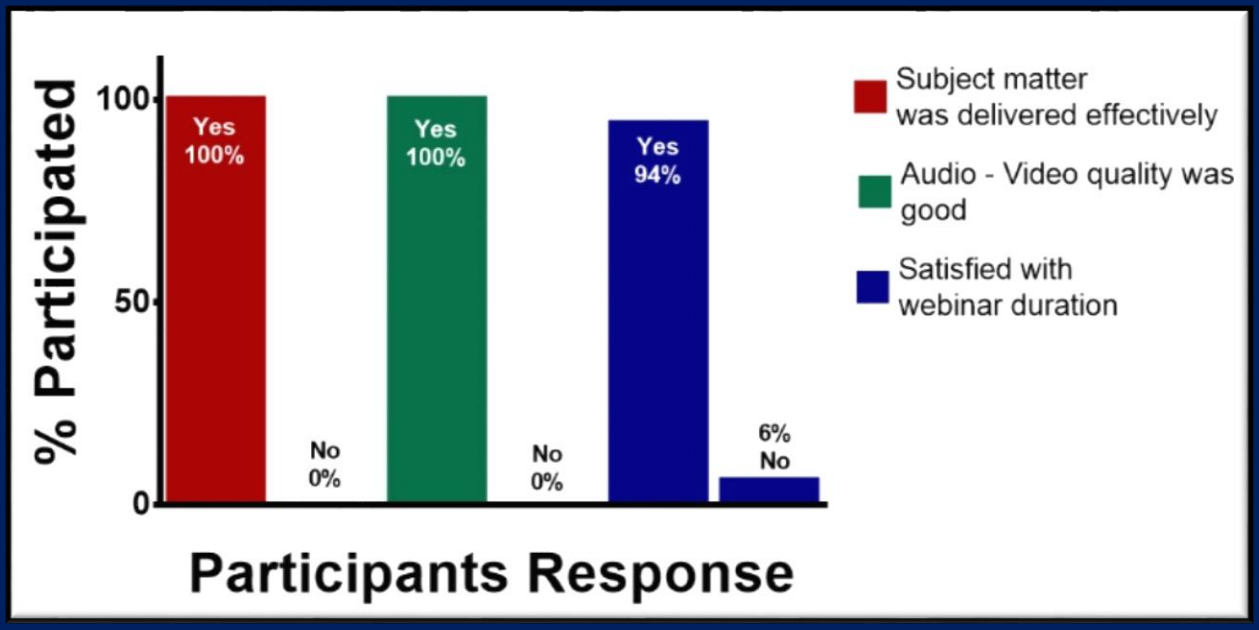
Not at all Satisfied
Participants Response


% Participated
100
50
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Yes
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Yes
94%
6%
No
Subject matter was delivered effectively
Audio - Video quality was good
Satisfied with webinar duration
Participants Response

Scientific Publishing Master Class

Practical recommendations to increase your chances of getting published

Dr Ishima Badhwar, MBBS, M Tech
Clinical Consultant

- MBBS

- M. Tech Biological Sciences & BioEngineering

- Research Manager Medical devices & Pharma

- Senior Customer Engagement Manager
- Clinical Consultant

Why is it important to publish science?

Because research and diffusion of knowledge are the fuel to a country's progress.

Because science that is not published does not exist.

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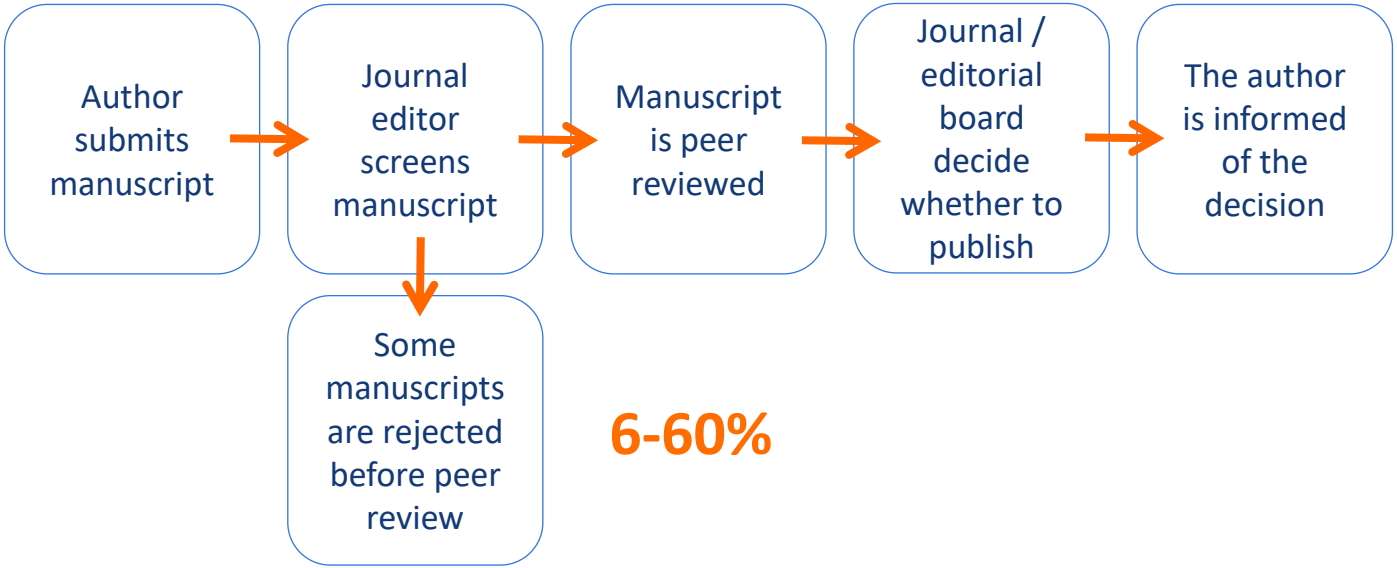
Goals

To provide you with **tools** and **practical recommendations** to write a **correct** scientific article to **improve** its chances of getting **accepted** for publication in a **peer-reviewed** journal.

Peer review and editorial process



http://www.editage.com/insights/peer-review-process-and-editorial-decision-making-at-journals

Publishing Tips

'Eight reasons I rejected your article'

A journal editor reveals the top reasons so many manuscripts don't make it to the peer review process

By Peter Thrower, PhD Posted on 12 September 2012

1. It fails the technical screening.
    - The English is not sufficient for the peer review process.
    - The figures are not complete or are not clear enough to read.
    - The article does not conform to the Guide for Authors for the journal it is submitted to.
    - References are incomplete or very old.
2. It does not fall within the Aims and Scope (of the journal).
3. It's incomplete.

https://www.elsevier.com/connect/8-reasons-i-rejected-your-article

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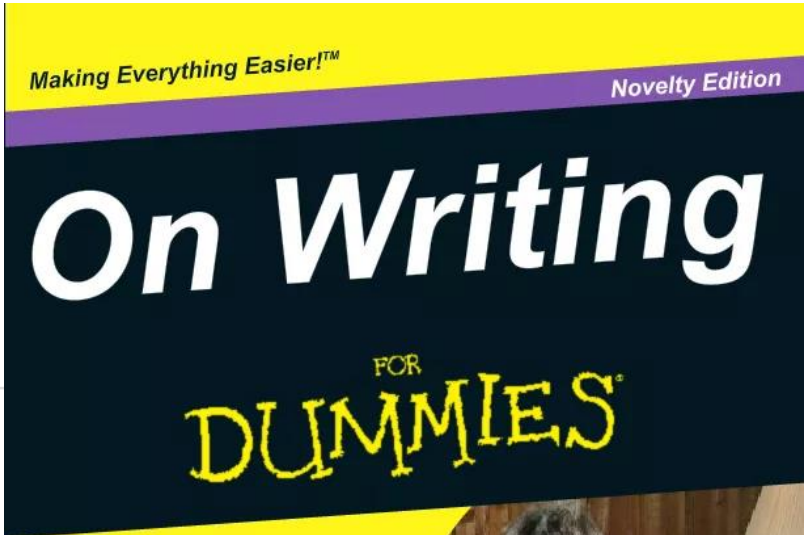
4. The procedures and/or analysis of the data is seen to be defective.
5. The conclusions cannot be justified on the basis of the rest of the paper..
6. It's is simply a small extension of a different paper, often from the same authors.
7. It's incomprehensible.
   - The language, structure, or figures are so poor that the merit can't be assessed. Have a native English speaker read the paper. Even if you ARE a native English speaker.
8. It's boring.

- That has **clear** and **useful** message
- That has a **logical** manner
- That is **easy** to read



- Original articles
- Review articles
- Case studies
- Letters, short communications
- Methods, procedures

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General structure of an original article

- Title
- Abstract
- Key words
- Introduction
- Methods
- Results
- Discussion and Conclusions
- Acknowledgements
- References
- Supplementary material

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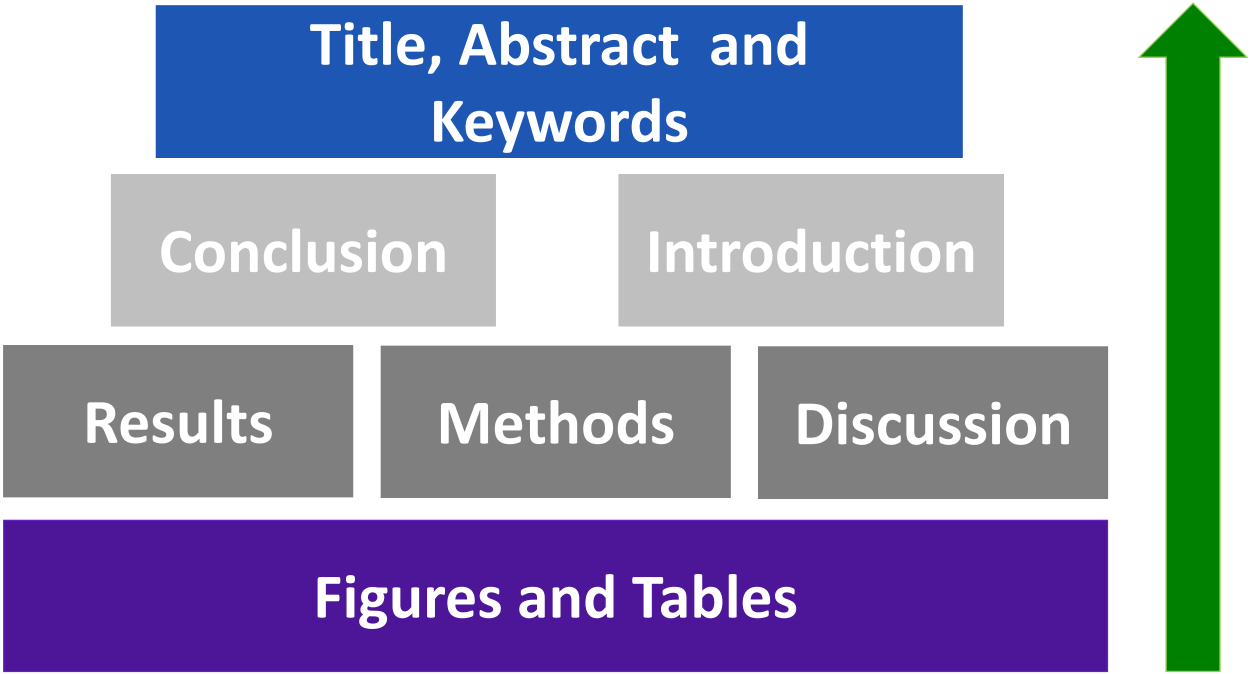
Title, Abstract and Keywords
Conclusion
Introduction
Results
Methods
Discussion
Figures and Tables

Tables and figures

- Play a **key** role in **improving** the manuscript's **quality**.
- Save **time** and **space** when representing numerical data.
- They significantly **reduce** the length of the manuscript.
- They provide the **editors**, **reviewers** and **readers** a quick **overview** of the study findings.
- They improve **understanding** and **interpretation** of the study results.

Table 3 Drug-related adverse events occurring in >10% of treatment cycles

	Grade 1–2		Grade 3–4	
Adverse event	**Patients *n* (%)**	**Cycles *n* (%)**	**Patients *n* (%)**	**Cycles *n* (%)**
Constitutional symptoms				
Fatigue	28 (78)	112 (53)	0 (0)	0 (0)
Hematologic				
Anaemia	21 (58)	111 (52)	1 (3)	1 (0.5)
Lymphopenia	19 (53)	112 (53)	1 (3)	2 (1)
Thrombocytopenia	18 (50)	61 (29)	1 (3)	1 (0.5)
Leukocytes	13 (36)	37 (17)	0 (0)	0 (0)
Metabolic				
Hyperglycaemia	17 (47)	92 (43)	8 (22)	24 (11)
Hypercholesterolaemia	13 (36)	68 (32)	2 (6)	7 (3)
Hypertriglyceridaemia	15 (42)	58 (27)	1 (3)	1 (0.5)
ALT	15 (42)	71 (33)	2 (6)	3 (1)
AST	20 (55)	71 (33)	1 (3)	1 (0.5)
ALP	6 (17)	28 (13)	1 (3)	1 (0.5)
Hypoalbuminaemia	9 (25)	35 (16)	0 (0)	0 (0)
Hypophosphataemia	8 (22)	35 (16)	4 (12)	15 (7)
Creatinine	13 (36)	33 (15)	0 (0)	0 (0)
Gastrointestinal				
Mucositis	26 (72)	71 (33)	0 (0)	0 (0)
Dysgeusia	10 (28)	47 (22)	0 (0)	0 (0)
Nausea	13 (36)	35 (16)	0 (0)	0 (0)
Diarrhoea	11 (30)	40 (19)	3 (9)	3 (1)
Constipation	10 (28)	28 (13)	0 (0)	0 (0)
Anorexia	13 (36)	31 (14)	0 (0)	0 (0)
Dermatologic				
Rash (desquamation)	22 (61)	104 (48)	1 (3)	3 (1)
Rash (acneiform)	16 (44)	76 (36)	0 (0)	0 (0)
Dry skin	12 (33)	40 (19)	0 (0)	0 (0)
Pruritus	9 (25)	38 (18)	0 (0)	0 (0)
Pulmonary				
Pneumonitis	7 (19)	35 (16)	0 (0)	0 (0)

Toxicity

Safety and tolerability data are available for 213 treatment cycles, with a median number of four cycles delivered per patient (range 1–21), AE deemed by the investigator as at least possibly related to

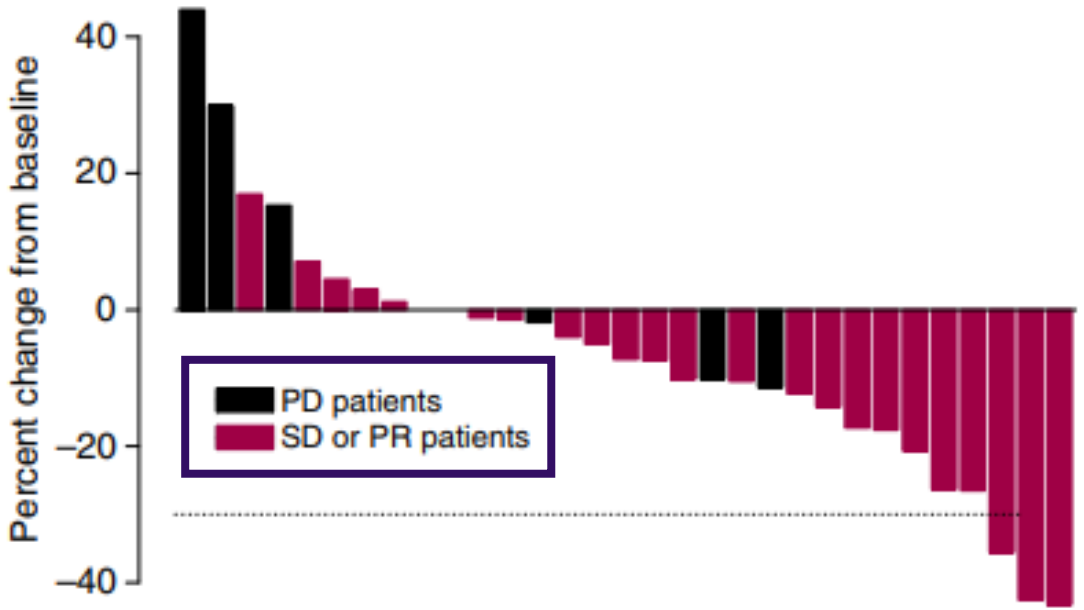

Figure 1 Maximal percentages of tumour reduction for target lesion(s) by RECIST criteria (*Note*: some patients with PD progressed owing to new or increasing non-target lesions, or by symptomatic progression).

Tables and figures

- First, design the **table**, then add the **labels**, and finally add the **numbers**.
- Use a **clean** layout and **legible** font.
- **Sufficient** spacing between **columns** and **rows**.
- **Do not** use **Power Point** to **format** tables or figures.
- **Do not** use special effects or 3D graphs.
- **Unify** decimal places:

0.162	0.2
3	3.0
0.001	<1

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- **Do not** forget the **title** or **legend**: they are **key** to **understanding** the table or figure.
- **Describe** in the **legend** any **abbreviations** and **symbols** used.
- Ensure **consistency** between **values** or **details** in the **table** and those in the **abstract** and **text** (print and compare). **Make sure the numbers add 100%.**
- For **submission**, leave one **table/figure** per **page**.

Results

- Answer the question **WHAT**.
- Written in **past** tense.
- Depending on the **type of study** they will need to include one type of **information** or **other**.
- **Use** http://www.equator-network.org/ to find guidelines, including STROBE and CONSORT.

RESULTS

Patients

A total of 37 patients were accrued to the study from January 2004 to July 2005. One patient did not receive any treatment owing to progressive disease before treatment initiation and was considerable ineligible. Thirty-six patients received at least one dose of temsirolimus and were evaluated for safety. Patient characteristics are listed in Table 1.

Efficacy

Tumour response Two patients, one with CT and one with ICC, achieved a confirmed PR. One of them progressed after 18 cycles (11.4 months after first observation of PR) and the other came off study owing to unrelated cardiac disease (4.5 months after first observation of PR). A third patient had an unconfirmed PR at the end of cycle 8 and discontinued therapy not owing to toxicity. Twenty additional patients had SD of at least 2 months' duration and among these, 10 patients continued treatment beyond six cycles. Ten patients progressed on temsirolimus without ever achieving an objective response. Eight of these patients had radiological evidence of disease progression, one had symptomatic progression during cycle 1, and one patient died of disease before end of cycle 2. Figure 1 shows the maximum percentage of target tumour lesion(s) reduction compared to baseline as assessed by the RECIST criteria, listed by individual study patients.

As serum markers such as chromogranin A or 5HIAA were not mandated in this protocol and not collected in all patients, the biochemical response could not be assessed.

The intent-to-treat response rate for the entire study cohort is 2/36 = 5.6% (95% CI 0.6–18.7%) and tumour control (SD + PR) rate is 23/36 = 63.9% (95% CI 46.2–79.2%). Response outcomes were similar between the CT and ICC histologies, with PR rates of 4.8 and 6.7%, respectively.

TTP Five patients remain on study and continue to receive treatment as of January 2006. Of the 31 patients who have come off treatment, the reasons for discontinuation were: PD (15), symptomatic PD (four), death (one), physician discretion (two), AE (seven) and patient withdrawal (two). Median TTP is estimated to be 6.0 months (95% CI 3.7-not reached); 6-month progression-free rate is estimated to be 48.1% (95% CI 33.0–70.1%) and 1-year progression-free rate is estimated to be 40.1% (95% CI 23.8–67.4%) (Figure 2).

Survival At the time of reporting, 11 patients have died. Median follow-up on the 25 patients alive at last follow-up is 13.9 months (range 2.8–22.6 months), minimum follow-up is 6.9 months. Median OS has not been reached; 6-month survival rate is estimated to be 91.6% (95% CI 82.9–100.0%) and 1-year survival rate is estimated to be 71.5% (95% CI 57.1–89.5%) (Figure 3). Patients with ICC appeared to have slightly better TTP and OS but statistical comparisons were not made for this subgroup analysis (Table 2).

Toxicity

Safety and tolerability data are available for 213 treatment cycles, with a median number of four cycles delivered per patient (range 1–21), AE deemed by the investigator as at least possibly related to

twice daily. To minimize the potential for angioedema, enalapril was withheld a day before starting LCZ696, and LCZ696 was withheld a day before starting randomized therapy. Patients tolerating both drugs at target doses were randomly assigned in a 1:1 ratio to double-blind treatment with either enalapril 10 mg twice daily or LCZ696 200 mg twice daily. The dose of enalapril was selected based on its effect to reduce the risk of death in the Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial[19]; higher doses have not been more effective or well tolerated during long-term treatment.[20–22] Following randomization, patients were maintained on the highest tolerated doses of the study medication. Surviving patients underwent periodic evaluation of NYHA functional class, symptoms of heart failure (measured by using the Kansas City Cardiomyopathy Questionnaire [KCCQ]),[23] and, in approximately 27% of randomized patients, biomarkers of neprilysin inhibition and heart failure progression. Worsening heart failure was treated by adjusting the doses of any concomitant drug and using any interventions that were clinically indicated.

Statistical Analysis

The trial was designed to recruit ≈8000 patients and continue until the occurrence of 1229 cardiovascular deaths and 2410 cardiovascular deaths or first hospitalizations for heart failure. However, an independent Data and Safety Monitoring Board recommended early termination of the study (approximately 50 months after the first patient was randomized) when the boundary for overwhelming benefit for cardiovascular mortality had been crossed.

The principal analyses for this article focused on (1) worsening NYHA functional class, as assessed by the physician; (2) worsening KCCQ total symptom score, as assessed by the patient; (3) worsening heart failure requiring an increase in the dose of diuretic for >1 month, the addition of a new drug for heart failure, or the use of intravenous therapy (prospectively defined in the protocol as a treatment failure); (4) worsening heart failure leading to an emergency department visit (without subsequent hospitalization); (5) worsening heart failure requiring hospitalization, with a prespecified analysis at 30 days after randomization; (6) the use of interventions for advancing heart failure; and (7) changes in biomarkers reflecting cardiac injury, wall stress, and the effects of neprilysin inhibition. All deaths and all hospitalizations possibly related to heart failure were adjudicated blindly according to prespecified criteria by a clinical-events committee, which had no knowledge of the patient's drug assignment. Of the 4 biomarkers of interest, plasma NTproBNP and troponin T were measured by using the Roche Elecsys proBNP and high-sensitivity Troponin T assays (Roche Diagnostics GmbH, Germany); plasma BNP was measured by using the Advia Centaur assay (Siemens, USA); and cGMP was measured in first-morning-void urine samples by using an enzyme-linked immunosorbent assay (R & D Systems

imputation was applied to patients who died or had missing data.

Results

Study Patients and Study Drug Administration

A total of 10521 patients at 1043 centers in 47 countries entered the run-in period, of whom 8399 patients were randomly assigned and prospectively included in the intention-to-treat analysis (4187 to LCZ696 and 4212 or enalapril). As previously reported,[12] the 2 groups comprised primarily patients with mild-to-moderate symptoms who were well treated with diuretics, β-blockers, and mineralocorticoid receptor antagonists and were balanced with respect to baseline characteristics. Excluding patients who died, 87% of both the LCZ696 and enalapril groups were receiving the target dose of the study drug at 8 months; and 76% and 75%, respectively, were maintained at the target dose at the end of the study.

Effect on Death or Hospitalization for Any Reason

There were 835 patients in the enalapril group and 711 in the LCZ696 group who died for any reason, corresponding to annualized rates of 7.5% and 6.0%, respectively. These differences reflected a 16% incremental reduction in the risk of death (hazard ratio, 0.84; 95% confidence interval [CI], 0.76–0.93, P=0.0009). There were 2093 patients who died or who were hospitalized for any reason in the enalapril group and 1892 such patients in the LCZ696 group, corresponding to annualized rates of 30.3% and 26.3%, respectively. These differences reflected a 12.6% lower risk as a result of treatment with LCZ696 instead of enalapril (hazard ratio, 0.87; 95% CI, 0.82–0.93; P<0.0001).

Effect on Occurrence of Clinical Worsening

In comparison with enalapril-treated patients, there were fewer LCZ696-treated patients who had worsening heart failure requiring the addition of a new drug, intravenous therapy, or an increase in the daily dose of diuretic for >1 month (520 versus 604; hazard ratio, 0.84; 95% CI, 0.74–0.94; P=0.003). Fewer patients in the LCZ696 group than in the enalapril

3. Results

3.1. Patients

Between May 2011 and December 2014, 86 patients (43 in the HX arm and 43 in the LX arm) from 28 institutions were enrolled in this study. All patients received the study treatment and were included in the efficacy and safety analyses (Fig. 1). Patient characteristics were balanced between the 2 arms, as shown in Table 1.

3.2. Efficacy

The median follow-up time was 44.6 months. The median PFS was 6.1 months in the HX arm and 7.1 months in the LX arm (stratified HR, 0.81; 90% confidence interval [CI], 0.55–1.21; $p = 0.39$; Fig. 2A). The median OS was 31.0 months in the HX arm and was not reached in the LX arm (stratified HR, 0.58; 95% CI, 0.26–1.31; $p = 0.18$; Fig. 2B). The ORR and DCR were evaluated in 77 patients (90%) with measurable lesions; the ORR was 40% (16/40) in the HX arm and 41% (15/37) in the LX arm ($p = 1.00$), and the DCR was 73% (29/40) in the HX arm and 92% (34/37) in the LX arm ($p = 0.038$), The proportion of patients with brain metastases as the site of first progression was 5% (2/43) in the HX arm and 5% (2/43) in the LX arm.

The subgroup analysis of PFS according to the baseline clinical characteristics showed similar results across all subgroups, except for the duration of prior systemic treatment for MBC (Fig. 3). The PFS benefit in the LX arm compared with the HX arm was significantly larger if the duration was less than 1 year (interaction $p = 0.007$; Fig. 4A and B). This result indicated that patients whose disease had progressed on trastuzumab-based therapy within one year benefited more from LX than from HX.

3.3. Treatment exposure and safety

The median duration of the study treatment was 5.3 months in the HX arm and 6.2 months in the LX arm. The relative dose intensity during the first 12 weeks of study treatment was 96.3% for trastuzumab and 80.1% for capecitabine in the HX arm and 89.0% for lapatinib and 84.1% for capecitabine in the LX arm.

Adverse events are listed in Table 2. Palmar-plantar erythrodysesthesia syndrome was the most common grade ≥ 3 adverse events in both arms. Diarrhea, rash, paronychia, and increased blood bilirubin were observed more in the LX arm. Five patients (12%) in the HX arm and 12 patients (28%) in the LX arm discontinued the study treatment because of adverse events. No treatment-related deaths were observed.

With regard to cardiac events, grade 3 left ventricular systolic dysfunction resulting from disease-related malignant pericardial effusion was observed in 1 patient in the HX arm, and grade 4 myocardial infarction and subsequent grade 4 heart failure was observed in 1 patient in the LX arm. These 2 patients recovered after appropriate treatment. No other cardiac adverse events were observed.

3.4. Post-study therapies

Most patients received post-study anticancer therapies, including anti-HER2 drugs, cytotoxic chemotherapy, and endocrine

Results

- Should **only** include the most **relevant** data.
- Must **not** include **results** whose **methods** have not been described**.**
- **Should** be the **consequence** of the **methods** used.
- **Must** answer the **questions** raised in the **Introduction**.
- Should be **easy** to **read** and **follow**.
- Must **not** include **results** that are **not** going to be **discussed**.

- Should **not** duplicate what is being presented in **Tables** and **Figures**.
- Use **numbered headings** and **subheadings** to group **similar** results.
- Double-check that **numbers** in the **text** match those in the **tables** and **abstract**.
- **Avoid** starting **phrases** with **numbers.**

Results

Of 195 patients screened, 83 (43%) were eligible for inclusion (figure 2). Baseline blood pressure characteristics were well matched in the two groups (table 1). Differences between groups were seen for some demographics; these probably have no clinical significant change in the control group (daytime: –1·5 [16·7] mm Hg systolic, p=0·60, and –1·1 [10·5] mm Hg diastolic, p=0·56; night-time: 3·0 [16·8] mm Hg systolic, p=0·30, and 2·5 [9·7] mm Hg diastolic, p=0·14).

17 patients (n=10 in the arteriovenous coupler group and n=7 in the control group) had previously undergone renal denervation beyond 6 months of enrolment. Those in the

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Methods

- Answer the question **HOW**.
- Written in **past tense**.
- Use http://www.equator-network.org/ as a guide.
- **Should** answer the following questions:
  - ✓ **Who?** Study population (inclusion and exclusion criteria).
  - ✓ **How**? Study design.
  - ✓ **Why?** What are we expecting to find? Outcomes.
  - ✓ **What** was done with the data? Statistical methods.

PATIENTS AND METHODS

Eligibility

Patients were eligible if they were 18 years of age or older and had histologically or cytologically confirmed NEC of either carcinoid or pancreatic ICC pathologies. Patients had to have documented progressive metastatic disease within 6 months of study entry. Previous chemotherapy, investigational agents, radioactive therapies and/or radiation were allowed if completed >4 weeks before study entry. Previous local therapy (e.g. bland or chemoembolisation) was allowed if completed >6 weeks before study entry. Patients were required to have measurable disease, an ECOG performance status ⩽2, normal serum cholesterol and triglyceride, adequate haematologic, hepatic, renal and cardiac functions and a life expectancy of >3 months. Patients had to have tumour lesions accessible for core biopsy, and must agree to undergo tumour biopsy before and 2 weeks after initiation of temsirolimus.

Treatment

Temsirolimus at 25 mg was administered as a 30-min intravenous infusion on a weekly schedule. Four weeks of treatment were considered as one cycle.

Assessment of toxicity

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

Dose modifications

Dose modifications of temsirolimus were based on haematologic and non-haematologic toxicities at the time of every weekly dose. Upon recovery of toxicity within a maximum delay of 3 weeks, temsirolimus may be re-started with a dose reduction. Stepwise dose modifications from 25 to 20, 15 and 10 mg were allowed, but doses once reduced cannot be re-escalated.

Response assessment

Radiological imaging was repeated every 8 weeks to assess for tumour response until disease progression, completion of study treatment or discharge of patient from study. Tumour responses were evaluated according to standard RECIST criteria (Therasse *et al*, 2000). Objective responses were confirmed by central independent radiological review.

Correlative studies

Archival tissues Archival paraffin slides were stained for PTEN, p53, pAKT, pS6 and pmTOR (phosphorylated mTOR) by immunohistochemistry. Slides were pretreated and incubated with primary antibody (Appendix 1), followed by biotin-conjugated secondaries and HRP-Streptavidin labelling reagent (ID Labs Inc.,

2.2. Patients

Eligible patients were women aged 20 years or older with HER2-positive MBC or unresectable locally advanced breast cancer who were previously treated with taxanes, with progression on trastuzumab-containing regimens. HER2 positivity was defined as 3 + staining by immunohistochemistry or *HER2* gene amplification (HER2:CEP17 signal ratio of 2.0 or more) by in situ hybridization. Patients treated with more than 2 chemotherapy regimens for MBC were excluded. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 and adequate bone marrow, cardiac, hepatic, and renal function. Patients with brain metastases were included if they were asymptomatic.

2.3. Endpoints

The primary endpoint was progression-free survival (PFS) and the secondary endpoints included overall survival (OS), the objective response rate (ORR), the disease control rate (DCR), the proportion of patients with brain metastases as the site of first progression, and safety. Tumor response and progression were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Chest/abdomen CT was performed at baseline and every 6 weeks. Brain MRI or CT was performed at baseline and every 6 weeks in patients with brain metastases and every 12 weeks in patients without brain metastases.

2.4. Analyses of PIK3CA mutations

Archival tumor tissues of primary lesions or metastases and plasma samples at enrollment were collected from all patients who gave their consent. DNA/RNA extraction from the formalin-fixed paraffin-embedded (FFPE) tumor tissues was performed using an

Methods

- **Do not** include **methods** that **do not** produce **results**.
- **Must not** include **introduction**, **results,** or **discussion**.
- **Should** contain enough **details** to **replicate** the methods.
- **Double check** that names of materials, equipment, reagents, genes, proteins used are correct.
- **Divide** them in (numbered) sections.
- **Lengthy** methods should be included **in references** or in "**supplementary materials/methods**" section.

Discussion

- It is the **most important** (and **hardest**) section to write.
- Many articles are **rejected** because the discussion is **weak**.
- Written in **past**, **present** and **future tense**.
- Answer the following **questions**:
  - Are my results **clinically** and **scientifically** relevant?

    The reader must be remined of the importance of what he/she just read.

- Are they **comparable** to other studies of **similar design**? (for example, similar disease, stage, dosage, treatment).
- If **not**, **why** not? Consideration of possible **mechanisms** and **reasons** for the **differences**.

- **Should** include study **limitations** and a **conclusion**. Both help **generate** new **ideas** for future **studies**.

Discussion

With the introduction of novel agents, thalidomide, bortezomib, and lenalidomide, most of the myeloma patients respond to induction therapy. Therefore, the next challenge is to maintain these responses, or even to improve them, to achieve prolonged PFS and, eventually, longer survival. Thus, maintenance therapy has become a field of increasing interest, and this may be particularly relevant for elderly patients because the advanced age as well as comorbidities and disabilities may potentially compromise the salvage therapies at the moment of disease progression and, therefore, the major benefit in outcome in the elderly population results from the initial approach of therapy. Here we report that the addition of a prolonged maintenance therapy with VT or VP results in a significant increase of the IF^{-} CR rate (42%) and a remarkably long PFS (35 months) with an acceptable toxicity profile.

Signaling Pathways Regulating Developmentally Programmed Senescence

Gene-expression analysis in the mesonephros suggested the upregulation of the TGF-β, Hedgehog, and WNT pathways in developmental senescence. We focused on the TGF-β pathway because of its previous involvement in senescence (Acosta et al., 2013; Kuilman and Peeper, 2009) and its well-established capacity to activate the transcription of the *p21* gene through SMAD complexes (Datto et al., 1995; Nakae et al., 2003; Reynisdóttir et al., 1995). We found high levels of phospho-SMAD2 (i.e., active) in the epithelia of the mesonephros and endolymphatic sac. Interestingly, treatment of pregnant females with a TGF-β pathway inhibitor significantly reduced SAβG activity and p21 levels, thus demonstrating a direct impact of the TGF-β pathway on p21-mediated senescence. TGF-β-activated SMAD proteins are known to act in concert with FOXO proteins (Seoane et al., 2004) and, based on this, we examined the impact of the PI3K/FOXO pathway on p21-mediated senescence. In

DISCUSSION

Essential Role of p21 in Developmentally Programmed Senescence

Here, we report that cellular senescence occurs at multiple locations during mammalian embryonic development. We have analyzed in detail the biological mechanisms and developmental significance of senescence in the regressing mesonephros and in the endolymphatic sac of the inner ear. Developmentally programmed senescence in these structures was defined by the presence of SAβG activity, heterochromatin markers (H3K9me3, HP1γ), and proliferative arrest (exclusion of Ki67). A number of senescence effectors were found expressed in the mesonephros and endolymphatic sac, namely p53, p21, p27, and p15. However, extensive genetic analyses indicated that only p21 was critical for developmental senescence at the studied structures (Figure 7E). Also, we could not detect evidence for DNA-damage markers in the senescent cells of the mesonephros and endolymphatic sac, nor an involvement of the DNA-damage-signaling kinases ATM or ATR. Therefore, developmentally

4. Discussion

4.1. What this study contributes to current knowledge

This study, conducted in two municipalities of northeast Brazil and central Colombia, and even though we should be cautious in generalizing the results, tackles a central policy concern for health systems: the access barriers encountered from the moment healthcare is sought through to resolution of the health problem, a

Colombia than in Brazil (69.9% and 53.9% respectively), followed by outpatient secondary care in Colombia (23.8%) and emergency services in Brazil (34.3% – notably different to Colombia's 20.9%) (Table 1).

3.2. Barriers in seeking healthcare

Of the episodes with a perceived healthcare need, 27.7% in Colombia and 16.2% in Brazil did not seek care (Table 1), this being more frequent in acute (32.8% in Colombia and 20.3% in Brazil) than in chronic episodes (12.7% in Colombia and 8.9% in Brazil). Furthermore, there were significant differences in Colombia between insurance schemes after adjustment for independent variables: healthcare was not sought in 15.7% of episodes in the special scheme, 21.1% in the contributory scheme, 30.6% in the subsidized scheme and in 57.7% of episodes among uninsured people. In Brazil, differences were mainly area specific: in Recife, 11.5% did not seek healthcare, compared to 20.9% in Caruaru.

The principal reasons for not seeking healthcare are related to the health services (Fig. 1a), primarily the long waiting times,

4.2. Significant barriers to seeking healthcare

In a considerable proportion of episodes, individuals with care needs do not seek healthcare in the areas studied in both countries, especially among enrolees in the subsidized scheme and uninsured people in Colombia and in the interior municipalities in Brazil. These figures are generally higher than those reported by the national surveys in Colombia (20.6%; (Profamilia, 2010) and for each scheme (26.0% for the uninsured, and 9.8% for the subsidized); (Departamento Administrativo Nacional de Estadística, 2009), and are similar to those reported by the National Household Sample Surveys in Brazil, 17.7% in 2008, which is much higher than that of

difference that may be due to the use of closed questions in those surveys, which limits users' responses and does not allow them to identify other more relevant reasons, such as enrolment problems, staff shortages, or appointment times in their health centres.

4.3. Barriers for entry to the health services

Although one would anticipate a lower proportion of refusals in a national health system with universal access than in a managed competition model in which the pursuit of profitability leads insurers and providers to impose barriers on access, our results obtained indicate quite the opposite. This may be due firstly to the high proportion of individuals in Colombia who decide not to seek care in order to avoid being rejected, and secondly to the barriers imposed by insurers within the services rather than at point of entry (Vázquez et al., 2012).

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Conclusion

- Written in **present tense**.
- Should be **directly** related to your **research question** and stated **purpose** of the study.
- Should be **based** on the **study results** described in the article.
- Should **convey** the **impact** of my **findings** (even if my results are negative).
- Should **not** be a copy of the **abstract**.
- Should **encourage** further **experiments**.

In conclusion, temsirolimus appears to have only modest activity with a manageable toxicity profile in advanced NEC. The results of this study do not warrant further investigation of this drug as a single agent in this patient population. Evaluation of temsirolimus, in combination with other targeted agents, such as a multi-kinase inhibitor or an antiangiogenic compound,

of isoniazid with moxifloxacin shortens tuberculosis treatment more than does replacement of ethambutol,[14] but human studies have not yet supported this finding.[26] The results of our study support the undertaking of clinical trials to assess whether shorter courses of moxifloxacin-containing regimens can cure tuberculosis as well as or better than the current 6-month regimen. Such trials are under way and their results are eagerly awaited.

Concluding Remarks

In summary, our findings expand the biology of cellular senescence from stress responses associated with pathological states, cancer, and aging to morphological processes during embryonic development in mammals. Developmentally programmed senescence is a physiological process that occurs

In summary, the addition of maintenance therapy with VT or VP to a short induction with VMP or VTP resulted in an increase of the ORR and IF^{-} CR rate, with an acceptable toxicity profile. Although no significant differences were observed between VT and VP, efficacy is in favor of VT and safety of VP. This approach was not able to overcome the adverse prognosis of high-risk CA. Finally, these bortezomib-based regimens as maintenance therapy may represent an optimal platform for further optimization of the treatment of elderly patients, particularly through the combination with lenalidomide that it is more potent and has a better safety profile than thalidomide.

Numerous ongoing studies are addressing different questions about optimal regimen, schedule, treatment duration, and route of drug delivery, and hopefully they will contribute to elucidate the final benefit of maintenance therapy to be implemented into routine clinical practice. Until these results become available, our current practice is to restrict maintenance therapies to patients enrolled into clinical trials.

Concluding Remarks

In summary, our findings expand the biology of cellular senescence from stress responses associated with pathological states, cancer, and aging to morphological processes during embryonic development in mammals. Developmentally programmed senescence is a physiological process that occurs

5. Conclusion

Accessing healthcare in the Colombian SGSSS and the Brazilian SUS is complicated, despite this being a central objective of the reforms introduced. Barriers to access appear throughout the trajectory, especially at the initial moment of seeking care and in health problem resolution in the case of the SGSSS, and in entry to services in the SUS. Although some common barriers were identified (waiting times or limited quality of the services), others are more specific to each health system. In the SGSSS, differential barriers to access include enrolment status and insurance scheme (care payments, and different benefit packages), or barriers related to intermediaries who do not guarantee geographical access or who use mechanisms such as the authorization of services to control access. In the SUS, refusal of care, prolonged waiting times related to the shortfall in human and physical resources are most important. The former barriers indicate the inexistence of a unified and universal social security in health system and failures in the market mechanisms introduced, despite 16 years of attempts to unify benefit packages and regulatory effort, and the latter highlight insufficient funding of the SUS to ensure universal coverage.

Finally, two new policy initiatives that may lead to an improvement in access barriers should be noted. First, in Colombia a new law has come into effect to equalize the benefits package in the two schemes (República de Colombia, 2012) and second Brazil recently introduced the "More Doctors Program", whose aim is to improve doctor availability in areas with shortage. The effect of theses two policy initiatives on access to healthcare should be the object of future analysis.

Introduction

- Answers the question **WHY**.
- Written in **present**, **past** and **present perfect tenses**.
- Should be **clear**, **engaging**, and **coherent**.
- It is **not** intended to be a **history lesson**.
- Should **not** include too many **references**.
- **Avoid** excessive **self-citation** and **self-reference.**

- Should answer the following questions:
  - ✓ What is **known**?
  - ✓ What is **not** yet **known**?
  - ✓ What is the **question** we are trying to **answer**?
  - ✓ **How** are we going to **answer it**?
- **Should** Include a **final paragraph** stating **why** is the study **important** or **interesting** (the study **objectives**).
- **Should** motivate the reader to continue reading.

1. Introduction

In recent decades, there has been impressive progress in the management of liver transplantation (LT), resulting in a constantly growing liver transplant recipient population, as reported by the last annual reports of the French Biomedicine Agency (2014) [1] and the OPTN (2012) [2–4]. Pre-existing chronic liver diseases

higher rate than in the general population [5–8]. Moreover, it is now well-known that the altered physiology and immunosuppression of these patients explain their increased exposure to postoperative complications. In this setting, it is safe to state that the progressively growing prevalence of the liver transplant target population has led to an increased rate of common surgical diseases. Taking into account the expected rise in live transplant survivors in coming years, an increase in further surgical procedures in this population is likely to lead significant problems for transplantation centers in terms of the allocation of beds, operating room availability and the use of hospital resources [5]. While most

complications and mortality are required for this specific patient population to managed them regarding medical and surgical care. The literature on the subject is very weak and insufficient, as only one benchmark study published in the past ten years ago has reported this specific aspect [6]. Therefore, an update on the epidemiology of post-LT surgical procedures seems relevant.

The aim of this monocentric retrospective cohort study was to assess the epidemiology of surgical procedures and their complications in the liver transplant recipient population to enhance their medical care.

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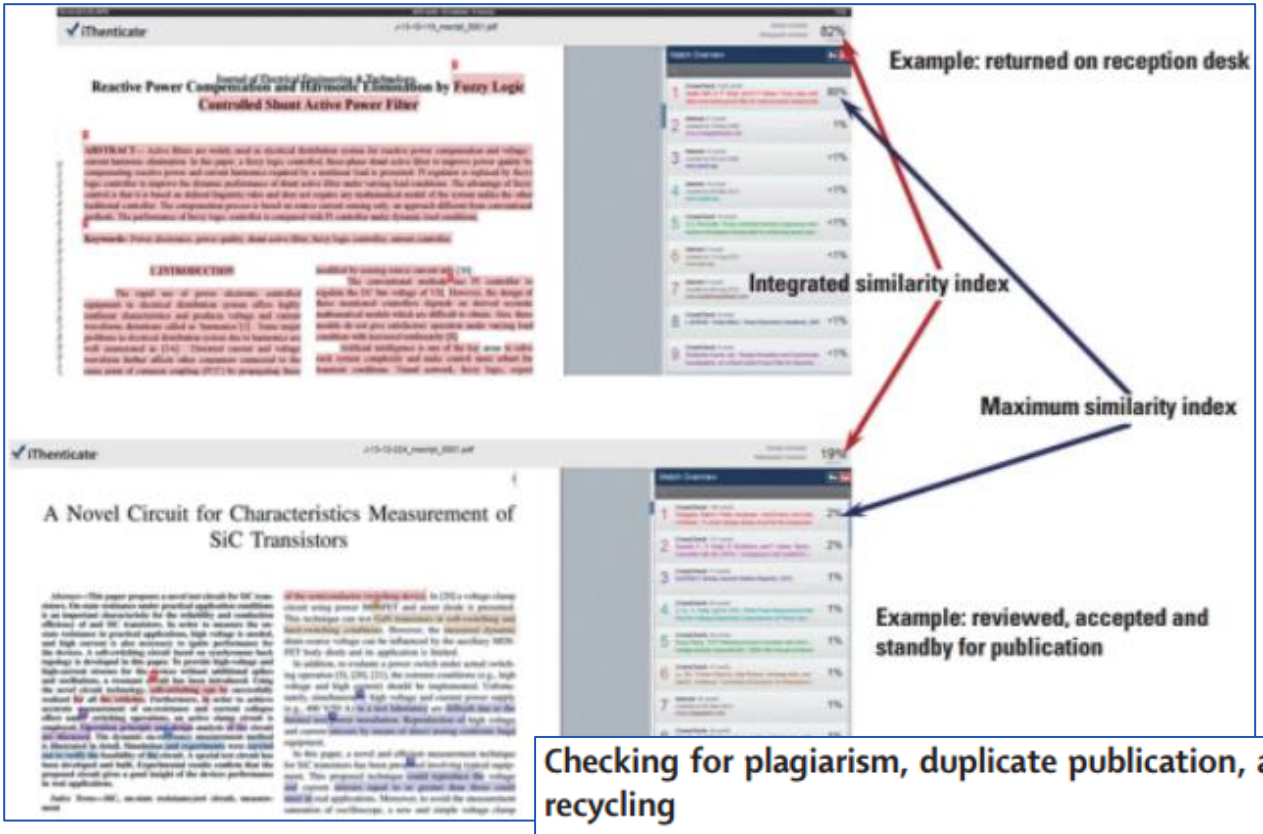

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- All Seminars, Series, Reviews, and other non-research material that we are interested in publishing will be checked by editors using CrossCheck (see *Lancet* 2011; **377:** 281–82). We expect that such papers are written in a way that offers new thinking without recycling previously published text

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Introduction

- Use **short** phrases (30-35 words).
- Write it in a way that it flows from **global** to **particular** ("our study").
- **Do not** include **results**, **discussion** or **conclusions**.
- **Write** it almost at the end, between the **discussion** and **abstract**.
- **Avoid** words like "***novel***", "***first time***", "***first ever***"...

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- **Avoid** starting phrases with an **abbreviation**, **acronym** or **number**.
- For **abbreviations**, apply the following **rule**: if **less than 5** throughout the manuscript, **do not** abbreviate or replace by an **acronym**.
- Use **widely** accepted **abbreviations** and **acronyms**.
- Review the **Guide for Authors** to determine the appropriate length.

References

- They usually contain more **mistakes** than any other section.
- Make sure you **know** the material you are **referencing**.
- **Include** references from **other** centers/regions.
- **Conform** strictly to the style given in the **Guide for Authors.**
- Use a **reference manager** to unify the style.
- Reference **key people** in the subject you are writing about.

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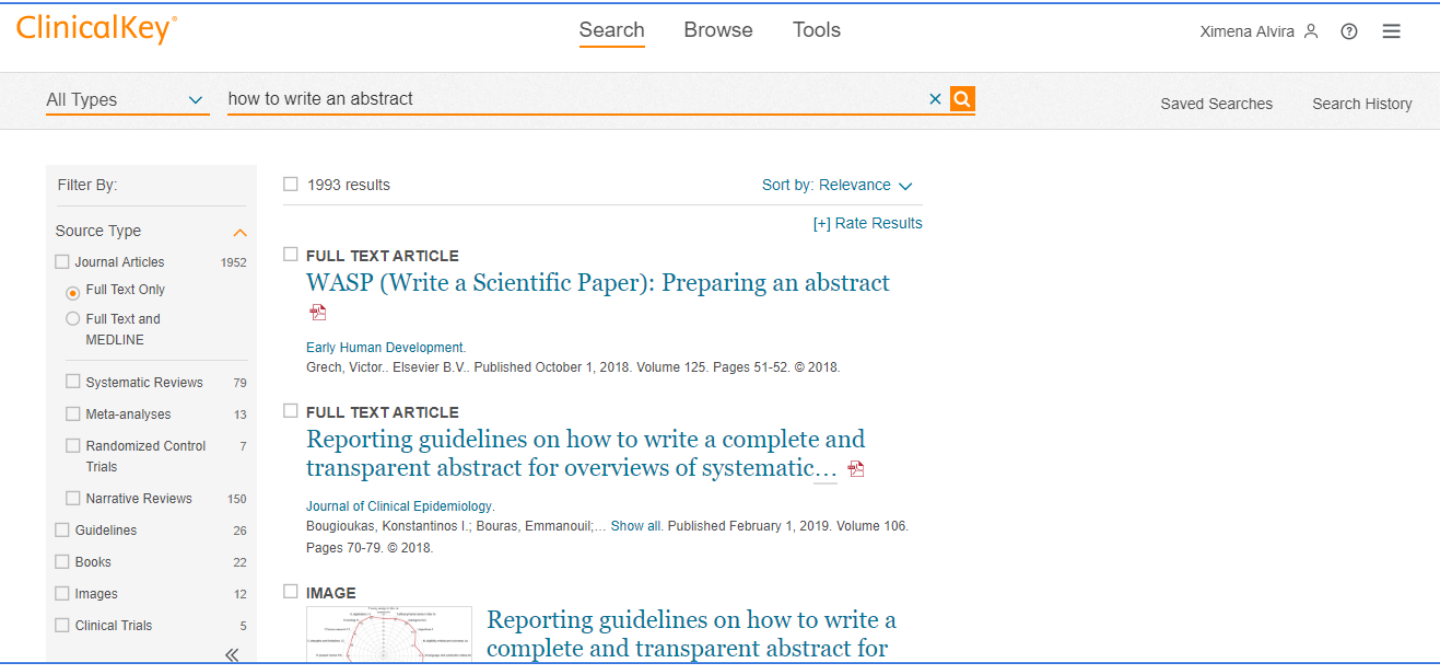

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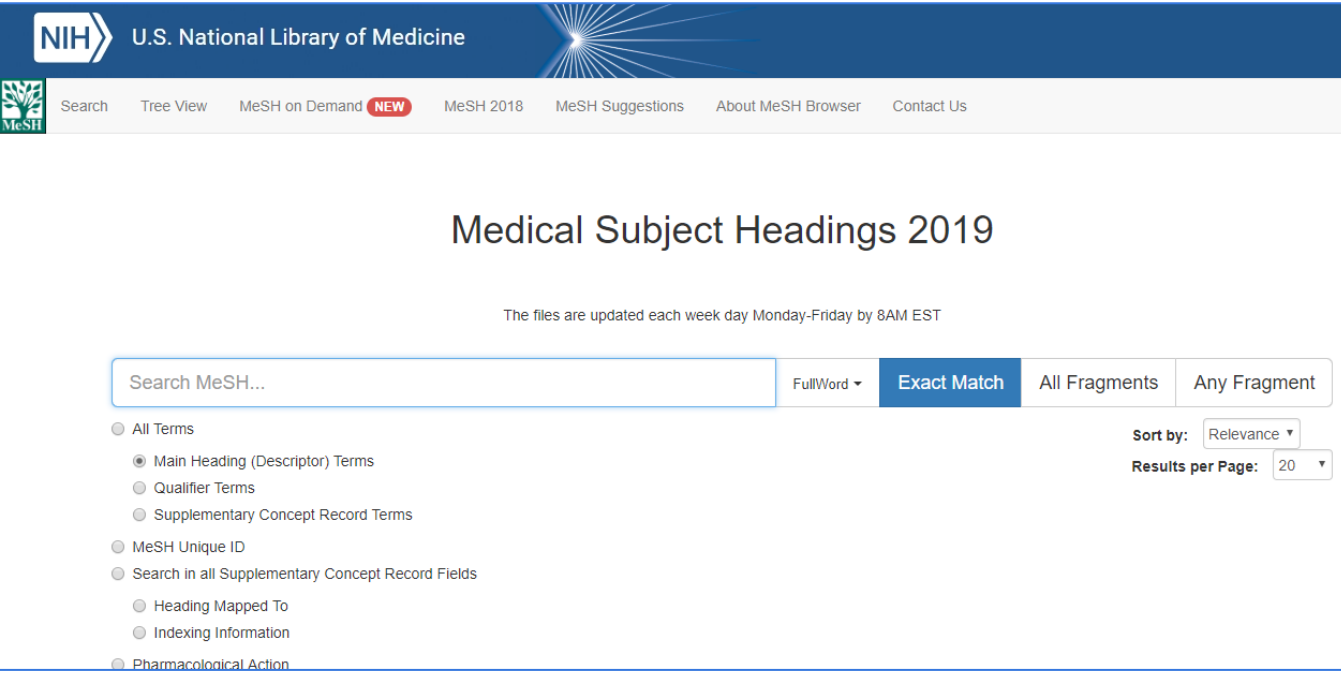

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Cover letter

- It can **strongly** influence the editor's decision.
- It is our greatest opportunity to speak directly to the editor.
- Concise, personal, honest, polite, professional.
- **Should** describe**:**
  - ✓ What we have done (main objective)
  - ✓ Why (rationale)
  - ✓ Why you believe your article is within the scope of the journal
  - ✓ What is novel about your work
- **Do not** copy-paste the abstract.

Dear Editor-in-Chief,

I am sending you our manuscript entitled "Techniques to detect circoviruses in Chinese bird species" by Bowler et al. We would like to have the manuscript considered for publication in the *Virology Journal*.

Please let me know of your decision at your earliest convenience.

With my best regards,

Sincerely yours,

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Dear Dr. Last Name:

I would like to submit the manuscript entitled "your article's name" by author names to be considered for publication as xxxxxxxxx[[paper type: "an original article", "a brief communication", "a case report"]] in the *Journal Name*.

xxxxxxxxx[[Summarize the research problem/gap, your main research findings, and the implications of your findings]]. We believe these findings will be of interest to the readers of your journal.

[[Revise or delete any of the following standard statements used in cover letters]]
We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We know of no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. As Corresponding Author, I confirm that the manuscript has been read and approved for submission by all the named authors.

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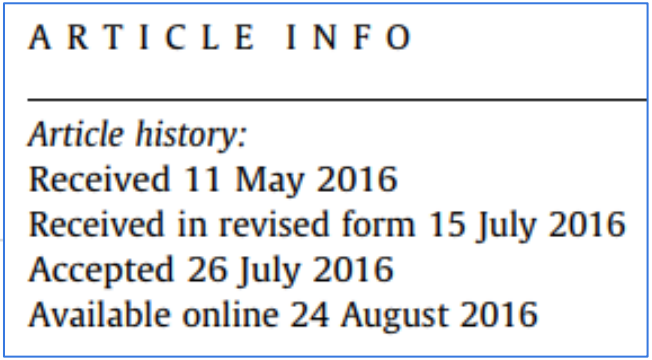
How to select the right journal?

- You **must** consider the journals' **aims** and **scope**, and make **sure** they match the **objectives** of your **study**.
- Consider **submitting** to journals included in the **studies** cited in your article.
- Consider the ***article history***.



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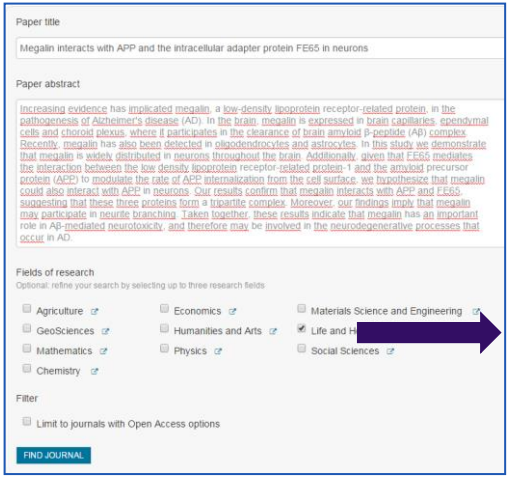

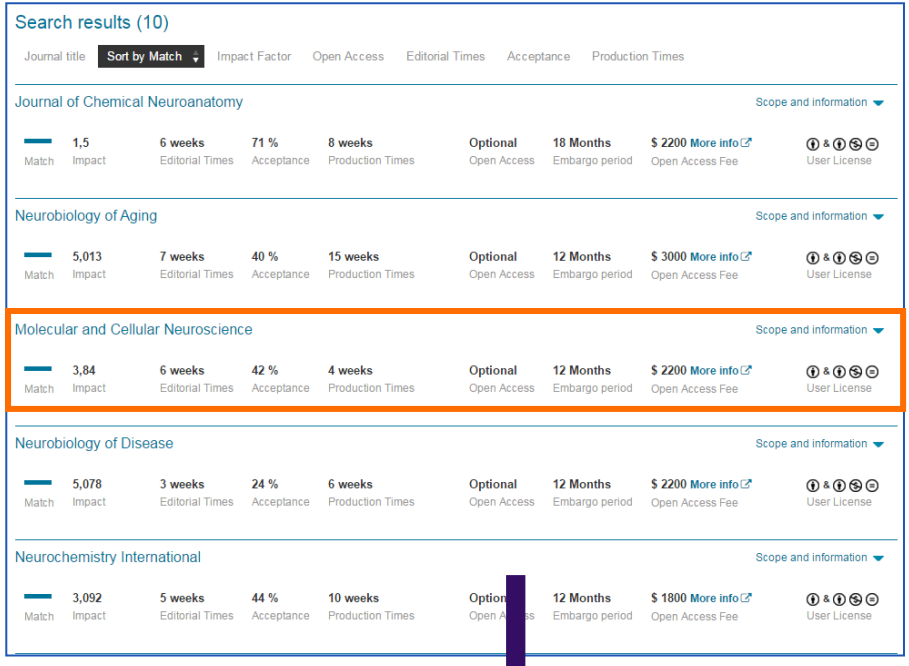

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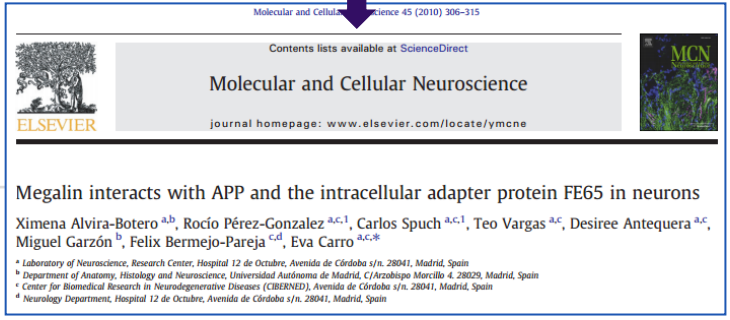

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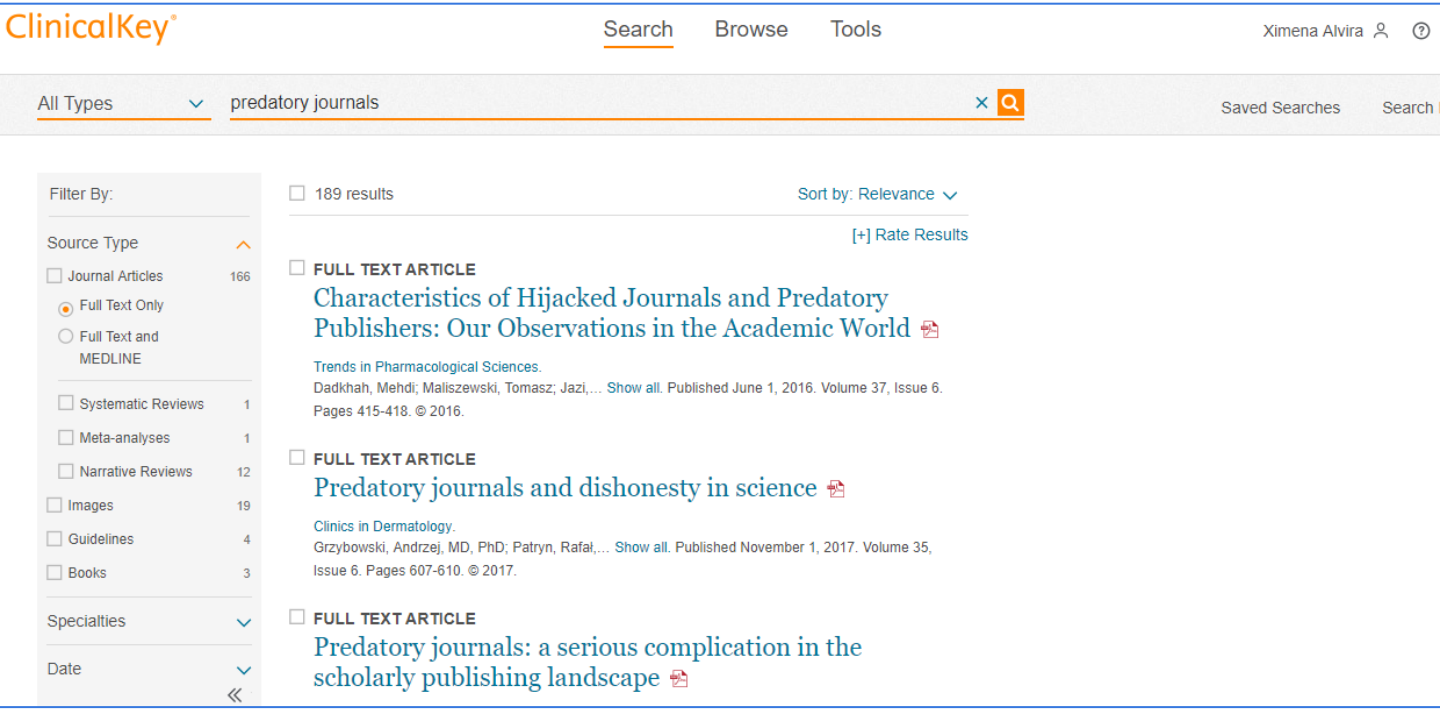

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Do not expect the editor or peer-reviewers to correct your "draft" manuscript

Just before sending:

- Review **every word** highlighted by the spell checker.
- Use **"Find"** function to replace every contraction with the fully spelled-out word (don't = do not; it's = it is).
- Use **"Find"** function to remove most **parentheses**; **except** when introducing **acronyms**, **numbering equations**, and presenting **alternate** measurement units.

- Make sure **acronyms** are **fully spelled** the first time they appear in the document.
- Double-check numbers in **text**, **tables**, **abstract**, **results** and **legends**.
- Perform **second level editing** by reading each sentence as an **independent** item.
- Use **“Replace”** function to remove multiple extra spaces between words.

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- **Check** once again that every **instruction** of the **Guide for Authors** is being **followed** (**print and cross out**).
- Finally, ask yourself **“is the document pretty?”**
- How does it look in **page preview**?
- Is there **enough** white space?
- Is there an **excess** of white space?

Publishing Tips

‘8 reasons I accepted your article'

Journal editors reveal the top reasons a manuscript gets published

By Elizabeth Zwaaf Posted on 15 January 2013

1. It provides insight into an important issue.
2. The insight is useful to people who make decisions.
3. The insight is used to develop a framework or theory, either a new theory or advancing an existing one.
4. The insight stimulates new, important questions.
5. The methods used to explore the issue are appropriate.
6. The methods used are applied rigorously and explain why and how the data support the conclusions.
7. Connections to prior work in the field or from other fields are made and serve to make the article's arguments clear
8. The article tells a good story, meaning it is well written and easy to understand, the arguments are logical and not internally contradictory.

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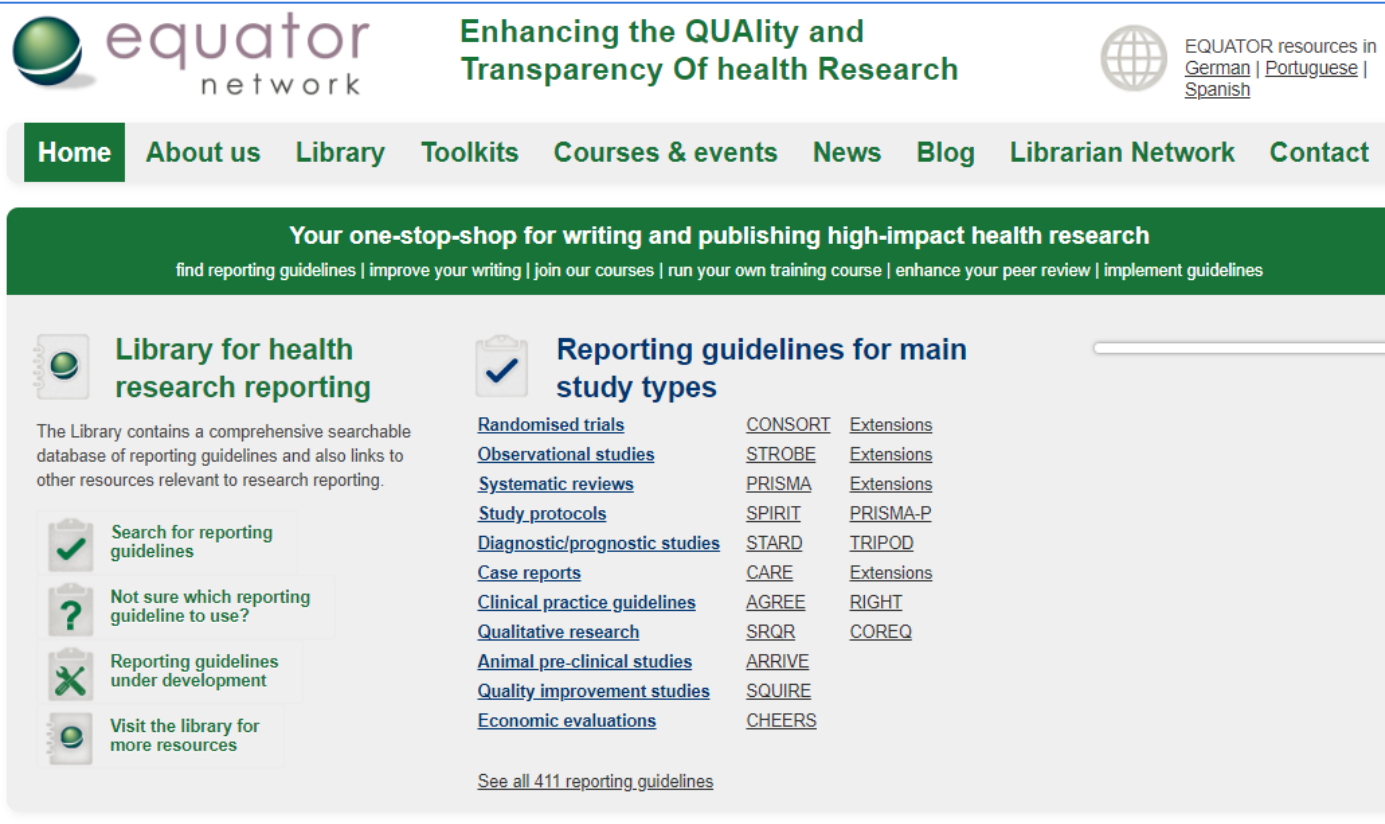

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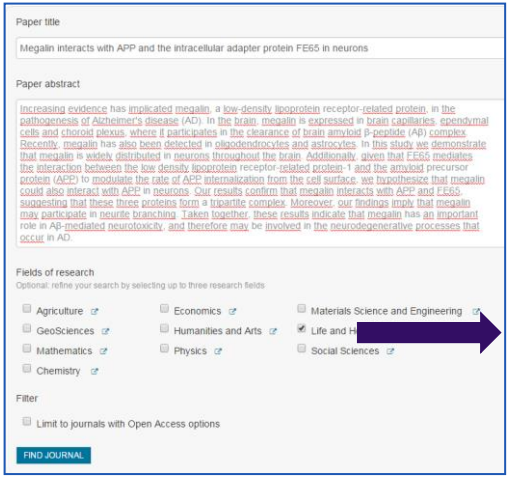

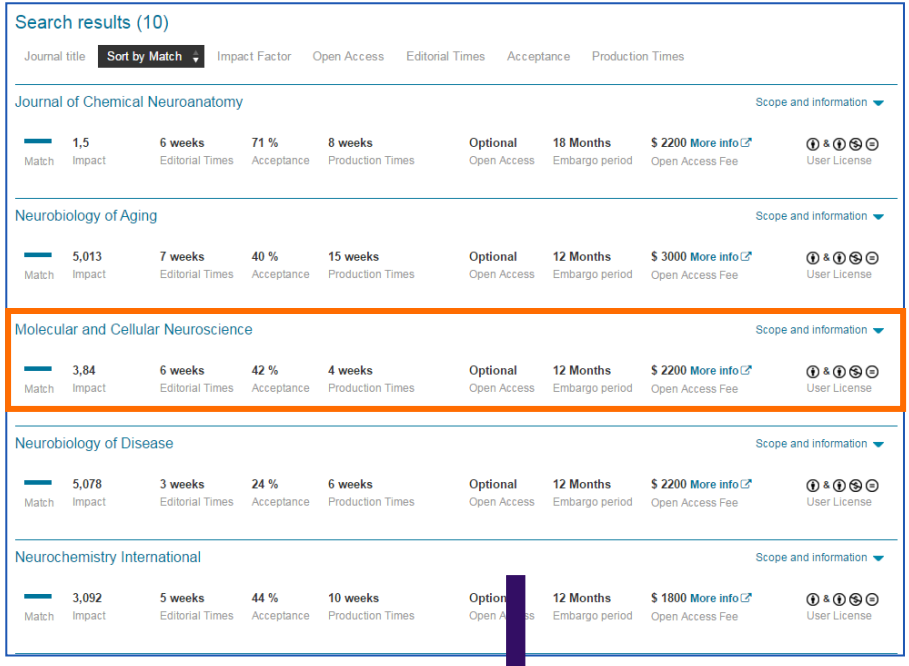

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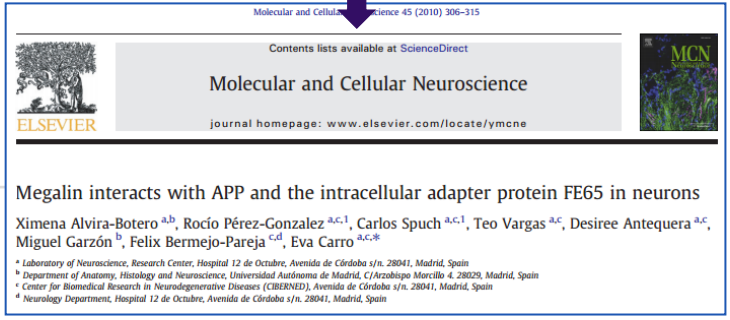

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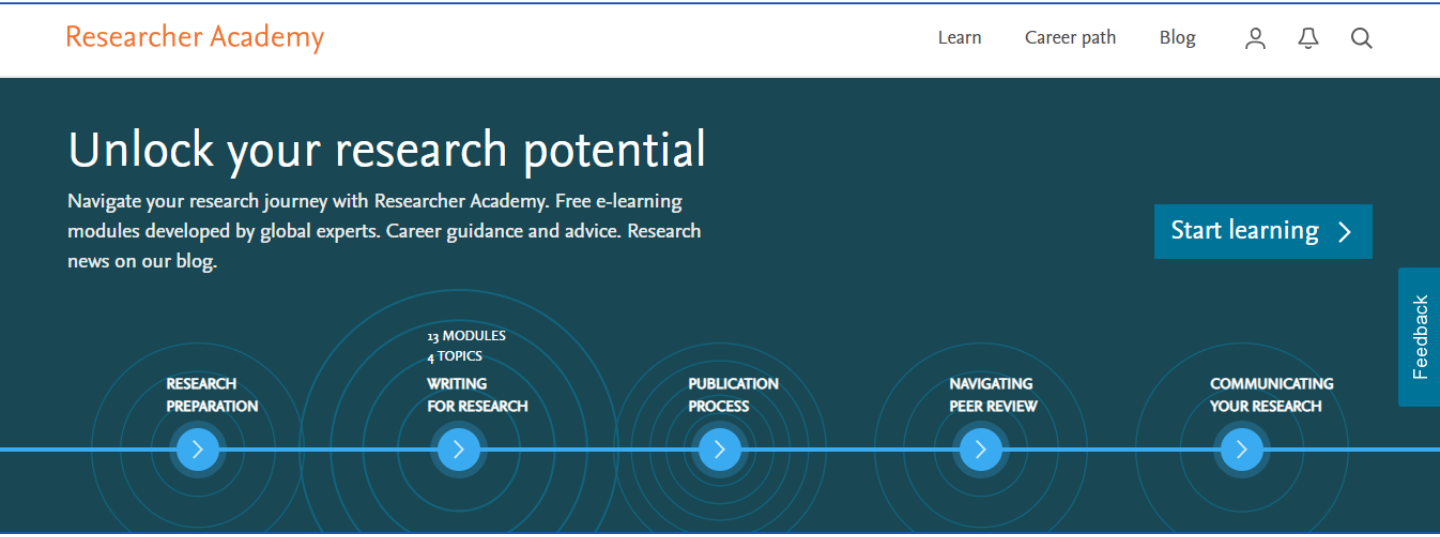

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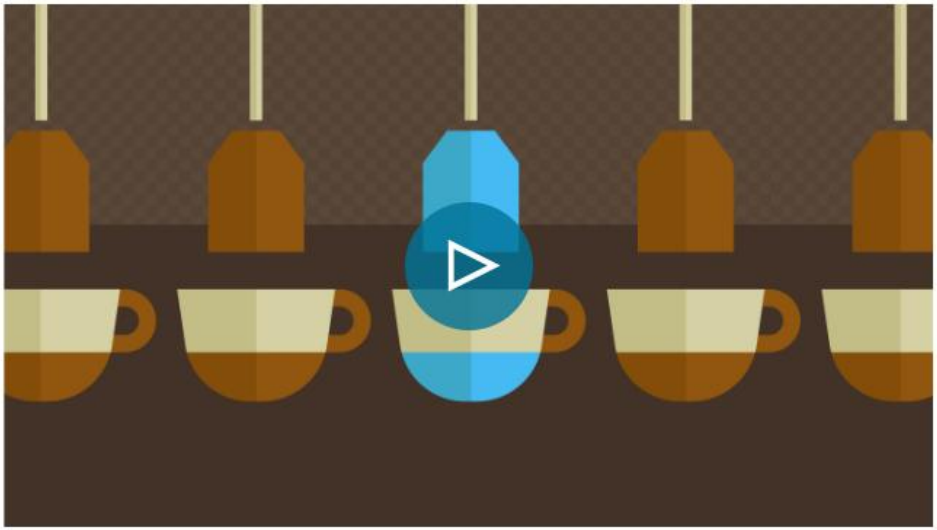
Seven strategies for scientists to communicate their research and create a brand



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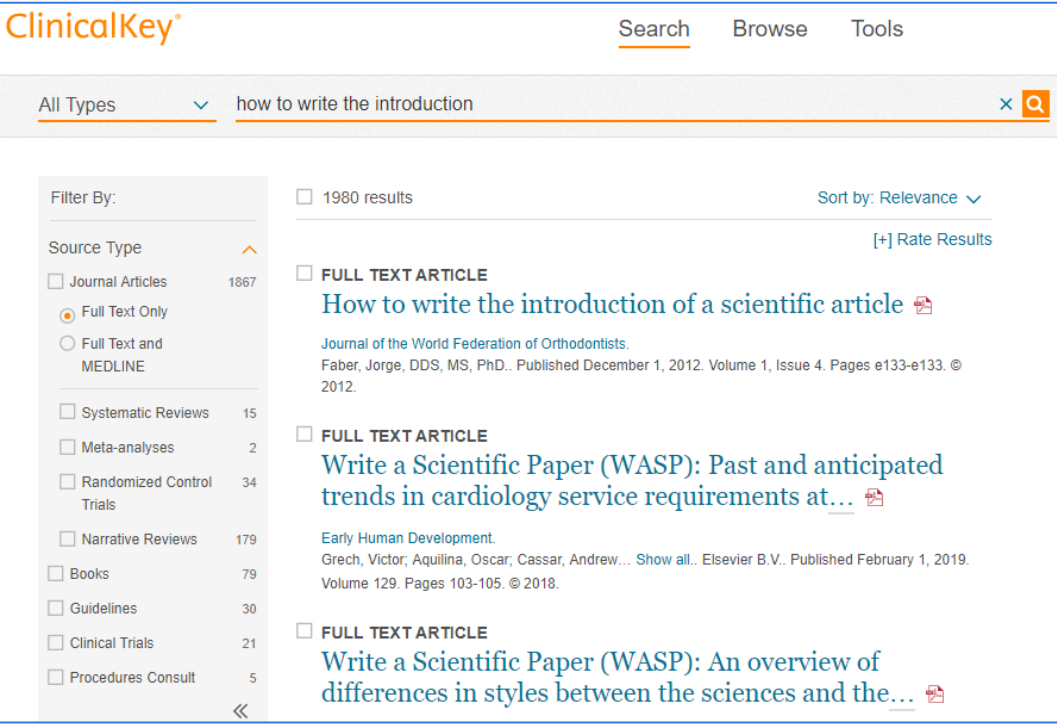

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